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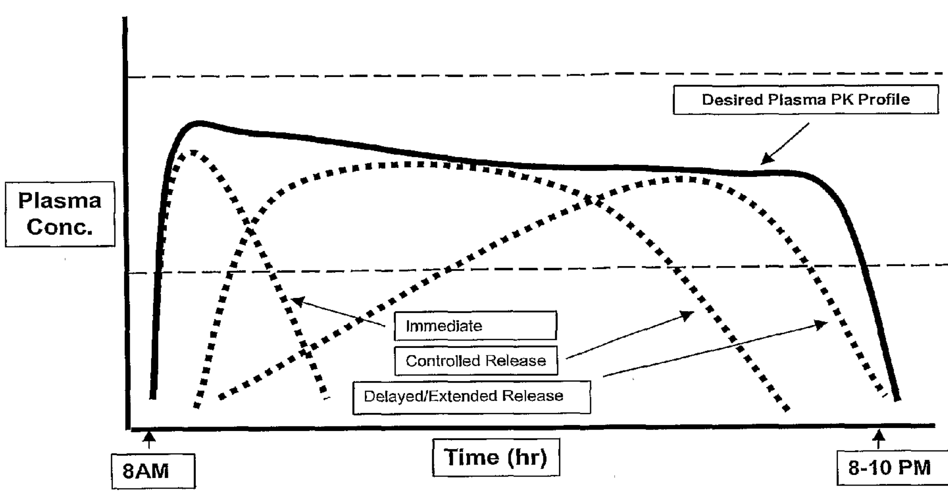

(57) Abstract: The invention relates to the improvement in the treatment of certain neural disorders / diseases, such as Parkinson's disease and other motor disorders. One aspect of the invention relates to drug compositions and dosage forms comprising said drug composition. Another aspect of the invention relates to methods of manufacturing the drug compositions and dosage forms. Another aspect of the invention relates to methods of treatment, comprising administering the drug composition and dosage form to an individual.

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IMPROVED DOSAGE FORMS FOR MOVEMENT DISORDER TREATMENT

Reference to Related Application

This application claims the benefit of the filing date of U.S. Provisional Application Serial No. 60/693,602, entitled "IMPROVED DOSAGE FORMS FOR MOVEMENT DISORDER TREATMENT," and filed on June 23, 2005. The teachings of the entire referenced application are incorporated herein by reference.

Background of the Invention

A movement disorder is a neurological disturbance that involves one or more muscles or muscle groups. Movement disorders affect a significant portion of the population, causing disability as well as distress. Movement disorders include Parkinson's disease, Huntington's chorea, progressive supranuclear palsy, Wilson's disease, Tourette's syndrome, epilepsy, tardive dyskinesia, and various chronic tremors, tics and dystonias. Different clinically observed movement disorders can be traced to the same or similar areas of the brain. For example, abnormalities of basal ganglia (a large cluster of cells deep in the hemispheres of the brain) are postulated as a causative factor in diverse movement disorders.

Parkinson's disease is a movement disorder of increasing occurrence in aging populations. It is a progressive neurodegenerative disorder affecting the mobility and control of the skeletal muscular system. The disease is associated with the depletion of dopamine from cells in the corpus striatum. Parkinson's disease is a common disabling disease of old age affecting about one percent of the population over the age of 60 in the United States. The incidence of Parkinson's disease increases with age and the cumulative lifetime risk of an individual developing the disease is about 1 in 40. Symptoms include pronounced tremor of the extremities, bradykinesia, rigidity and postural change. A perceived pathophysiological cause of Parkinson's disease is progressive destruction of dopamine-producing cells in the basal ganglia which comprise the pars compartum of the substantia nigra, basal nuclei located in the brain stem. Loss of dopamineric neurons results in a relative excess of acetylcholine. See Jellinger, *Post Mortem Studies in Parkinson's Disease - Is It Possible to Detect Brain Areas For Specific Symptoms*?, *J. Neural. Transm.*

56(Supp): 1-29:1999. Parkinson's disease often begins with mild limb stiffness and infrequent tremors and progresses over a period of ten or more years to frequent tremors and memory impairment, to uncontrollable tremors and dementia.

Tardive Dyskinesia (TD) is a chronic disorder of the nervous system, characterized by involuntary, irregular rhythmic movements of the mouth, tongue, and facial muscles. The upper extremities also may be involved. These movements may be accompanied, to a variable extent, by other involuntary movements and movement disorders. These include rocking, writhing, or twisting movements of the trunk (tardive dystonia), forcible eye closure (tardive blepharospasm), an irresistible impulse to move continually (tardive akathisia), jerking movements of the neck (tardive spasmodic torticollis), and disrupted respiratory movements (respiratory dyskinesia). The vast majority of TD cases are caused by the prolonged use of antipsychotic drugs (neuroleptics). A relatively small number are caused by the use of other medications, such as metoclopramide, that, like neuroleptics, block dopamine receptors. TD often manifests or worsens in severity after neuroleptic drug therapy is discontinued. Resumption of neuroleptic therapy will temporarily suppress the involuntary movements, but may aggravate them in the long run.

TD affects approximately 15-20% of patients treated with neuroleptic drugs (Khot *et al.*, *Neuroleptics and Classic Tardive Dyskinesia*, in Lang AE, Weiner WJ (eds.): *Drug Induced Movement Disorders*, Futura Publishing Co., 1992, pp 121-166). Therefore, the condition affects hundreds of thousands of people in the United States alone. The cumulative incidence of TD is substantially higher in women, in older people, and in those being treated with neuroleptics for conditions other than schizophrenia, such as bipolar disorder (manic-depressive illness) (see, *e.g.*, Hayashi *et al.*, *Clin. Neuropharmacol.* **19**: 390, 1996; Jeste *et al.*, *Arch. Gen. Psychiatry* **52**: 756, 1995). Unlike the acute motor side effects of neuroleptic drugs, TD does not respond in general to antiparkinson drugs (Decker *et al.*, *New Eng. J Med.* Oct. 7, p. 861, 1971).

Focal Dystonias (FD) are a class of related movement disorders involving the intermittent sustained contraction of a group of muscles. The prevalence of focal dystonias in one US county was estimated as 287 per million (Monroe County Study); this suggests that at least 70,000 people are affected in the US alone. The spasms of focal dystonia can last many seconds at a time, causing major disruption of the function of the affected area. Some of the focal dystonias are precipitated by repetitive movements; writer's cramp is the best known example. Focal dystonia can involve the face (*e.g.*, blepharospasm, mandibular

dystonia), the neck (torticollis), the limbs (*e.g.*, writer's cramp), or the trunk. Dystonia can occur spontaneously or can be precipitated by exposure to neuroleptic drugs and other dopamine receptor blockers (tardive dystonia). No systemic drug therapy is generally effective, but some drugs give partial relief to some patients. Those most often prescribed are anticholinergics, baclofen, benzodiazepines, and dopamine agonists and antagonists. The most consistently effective treatment is the injection of botulinum toxin into affected muscles.

The various focal dystonias tend to respond to the same drugs (Chen, *Clin. Orthop.* June 102-6, 1998; Esper *et al.*, *Tenn. Med.* **90**: 18-20, 1997; De Mattos *et al.*, *Arq Neuropsiquiatr* **54**: 30-6, 1996). This suggests that a new treatment helpful for one focal dystonia would be likely to be helpful for another. Furthermore, the common symptoms, signs, and responses to medication of spontaneous (idiopathic) dystonia and neuroleptic-induced dystonia suggest that an effective treatment for a drug-induced focal dystonia will be effective for the same dystonia occurring spontaneously.

A tic is an abrupt repetitive movement, gesture, or utterance that often mimics a normal type of behavior. Motor tics include movements such as eye blinking, head jerks or shoulder shrugs, but can vary to more complex purposive-appearing behaviors such as facial expressions of emotion or meaningful gestures of the arms and head. In extreme cases, the movement can be obscene (copropraxia) or self-injurious. Phonic or vocal tics range from throat clearing sounds to complex vocalizations and speech, sometimes with coprolalia (obscene speech) (Leckman *et al.*, *supra*). Tics are irregular in time, though consistent regarding the muscle groups involved. Characteristically, they can be suppressed for a short time by voluntary effort.

Tics are estimated to affect 1% to 13% of boys and 1% to 11% of girls, the male-female ratio being less than 2 to 1. Approximately 5% of children between the ages of 7 and 11 years are affected with tic behavior (Leckman *et al.*, *Neuropsychiatry of the Bas. Gang* **20(4)**: 839-861, 1997). The estimated prevalence of multiple tics with vocalization, *e.g.*, Tourette's syndrome, varies among different reports, ranging from 5 per 10,000 to 5 per 1,000.

Gilles de la Tourette syndrome (TS) is the most severe tic disorder. Tourette's syndrome is 3-4 times more common in boys than girls and 10 times more common in children and adolescents than in adults (Leckman *et al.*, *Neuropsychiatry of the Bas. Gang* **20(4)**: 839-861, 1997; Esper *et al.*, *Tenn. Med.* **90**: 18-20, 1997). Patients with TS have

multiple tics, including at least one vocal (phonic) tic. TS becomes apparent in early childhood with the presentation of simple motor tics, for example, eye blinking or head jerks. Initially, tics may come and go, but in time tics become persistent and severe, and begin to have adverse effects on the child and the child's family. Phonic tics manifest, on average, 1 to 2 years after the onset of motor tics. By the age of 10, most children have developed an awareness of the premonitory urges that frequently precede a tic. Such premonitions may enable the individual to voluntary suppress the tic, yet premonition unfortunately adds to the discomfort associated with having the disorder. By late adolescence/early adulthood, tic disorders can improve significantly in certain individuals. However, adults who continue to suffer from tics often have particularly severe and debilitating symptoms. (Leckman *et al.*, *Neuropsychiatry of the Bas. Gang* **20(4)**: 839-861, 1997).

Although the present day pharmacopeia offers a variety of agents to treat movement disorders, none of these agents can prevent or cure these conditions. Many treatments focus on eliminating or at least alleviating certain symptoms of the disorder. Furthermore, the most effective treatments are often associated with intolerable side effects. There remains a clear-cut need for new treatments for movement disorders that have greater efficacy and fewer side effects than those currently available.

For example, Parkinson's disease (PD) is associated with the depletion of dopamine from cells in the corpus striatum. Since dopamine can't cross the blood brain barrier (BBB), it is ineffective in the treatment of Parkinson's disease. Levodopa, a metabolic precursor of dopamine, readily crosses the BBB, and is metabolically transformed to dopamine by the aromatic L-amino acid decarboxylase enzyme. This enzyme is found throughout the body including gastric juices and the mucosa of the intestine. Thus, treatment with levodopa alone requires administration of large doses of the drug due to extracerebral metabolism by this enzyme. The resulting high concentration of extracerebral dopamine causes nausea in some patients. To overcome this problem, levodopa is usually administered with an inhibitor of the aromatic L-amino acid decarboxylase enzyme such as carbidopa, which cannot itself cross the blood brain barrier and has no effect on the metabolism of levodopa in the brain. The levodopa / carbidopa therapy is considered to be the most effective treatment for symptoms of Parkinson's disease (*The Medical Letter* **35**: 31-34, 1993). Nevertheless, certain limitations become apparent within two to five years of initiating combination therapy. As the disease progresses, the benefit from each dose becomes shorter

("the wearing off effect"), and some patients fluctuate unpredictably between mobility and immobility ("the on-off effect"). "On" periods are usually associated with high plasma levodopa concentrations and often include abnormal involuntary movements, *i.e.*, dyskinesias. "Off" periods have been correlated with low plasma levodopa and bradykinetic episodes.

A second problem for the multiple dose regimen is that the "peak and trough" blood levels produced by multiple daily doses result in fluctuating stimulation of the dopaminergic neurons. These fluctuations may contribute to the pathogenesis of the motor complications in Parkinson disease. For example, commonly occurring adverse effects associated with MIRAPEX® (a marketed PD drug) include nausea, vomiting / emesis, weakness, dizziness, fainting, agitation, confusion, hallucinations, muscle twitching, uncontrollable movements, a tingling sensation, chest pain, insomnia, somnolence, decreased appetite, dry mouth, sweating, headache, constipation and gastric intestinal complications.

Therefore, there is a need to develop new and improved dosage forms to treat various movement disorders, such as using levodopa / carbidopa in alleviating at least one adverse effect associated with the treatment of Parkinson's disease.

Summary of the Invention:

The present invention is directed to dosage forms that allow drug to be released in a highly controlled, time-dependent manner.

In general, any of the subject dosage forms and/or delivery devices (such as those described in the figures) may be used to deliver any of a large spectrum of compounds (*e.g.*, drugs, prodrugs, metabolic precursors, *etc.*), especially those with limited absorption windows in upper GI (*e.g.*, stomach).

An exemplary list of compounds that can be delivered using the subject dosage forms and/or delivery devices includes, but not limited to: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane, sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine, domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycin, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam,

ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts of the above.

One aspect of the invention relates in general to any drug that may be used to treat Parkinson's disease (or other movement disorders), especially levodopa / carbidopa therapy using the subject dosage forms and delivery devices.

Preferably, the drugs or prodrugs are released at a rate that results in reduction in the frequency or severity of at least one adverse effect associated with levodopa / carbidopa therapy.

In one embodiment, the dosage form releases levodopa and carbidopa at a rate that results in reduction in the frequency or severity of at least one adverse event associated with current levodopa / carbidopa therapies, or allows for a more convenient dosing regimen than current therapies.

As used herein, wherever reference to an effective composition (*e.g.*, "levodopa" or "carbidopa") is made, it should be understood that the effective composition may include drug and/or prodrug. In other words, any drug may be replaced in whole or in part by its prodrug(s), metabolic precursor(s), or analog(s) that provides the same therapeutic effect.

Thus, generally, one aspect of the invention provides a single dosage formulation of a pharmaceutical composition for treatment of a movement disorder. The single dosage formulation comprises levodopa and/or a metabolic precursor thereof, and optionally a decarboxylase enzyme inhibitor, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa thereof over a period of at least about 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours or more.

In one embodiment, the pharmaceutical composition comprises: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient within about 2 hours of administration to the patient (*e.g.*, less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration

of levodopa or the precursor in the patient; wherein at least the first IR portion further comprises a decarboxylase enzyme inhibitor, and the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

In certain embodiments, the first immediate-release (IR) portion reaches half-maximum dissolution (*e.g.*, when 50% of the effective composition is released) within about 1 hour, 30 minutes, 15 minutes, 10 minutes, or 5 minutes or less.

In certain embodiments, the pharmaceutical composition further comprises: (3) a substantially ascending release portion comprising levodopa or a metabolic precursor thereof, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

In certain embodiments, the pharmaceutical composition further comprises: (4) a substantially elevating release portion comprising levodopa or a metabolic precursor thereof, formulated to elevate the substantially zero-order release rate to a higher level beginning around a predetermined time point, such as about 3-7, 4-7, or 4-6 hours after administration to the patient.

In certain embodiments, at the end of the treatment period, the substantially elevating release portion is optionally formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration. This may be effected by, for example, using a similar second immediate-release portion described above.

In certain embodiments, the substantially elevating release portion comprises a decarboxylase enzyme inhibitor.

In certain embodiments, the substantially elevating release portion comprises levodopa or the precursor.

As used herein, "substantially ascending release portion" is an optional portion of the subject single dosage formulation pharmaceutical composition, which release profile resembles a peak, *e.g.*, having sloping ascending and descending slopes with substantially no intervening plateau at which the release is maintained at a substantially constant rate. The ascending and descending slopes of the peak may be, but need not be asymmetrical. In certain embodiments, the ascending slope may be quite steep, *e.g.*, the substantially ascending release portion may be a second immediate release portion, *e.g.*, as a delayed-release immediate release portion. In other embodiments, the substantially ascending release portion may adopt a substantially milder ascending slope than that of the first immediate

release portion, *e.g.*, as a delayed-release controlled-release portion.

As used herein, "substantially elevating release portion" is an optional portion of the subject single dosage formulation pharmaceutical composition, which release profile resembles a plateau, *e.g.*, having an ascending slope, a relatively flat plateau, and a descending slope. The plateau is "elevated," in that the relative constant level of levodopa is higher than the previous substantially zero-order release rate. The ascending and descending slopes of the peak may be, but need not be, asymmetrical. In certain embodiments, the ascending slope may be quite steep, *e.g.*, the substantially ascending release portion may be a second immediate release portion, *e.g.*, as a delayed-release immediate release potion. In other embodiments, the substantially ascending release portion may adopt a substantially milder ascending slope than that of the first immediate release portion, *e.g.*, as a delayed-release controlled-release portion.

As used herein, "rapid" refers to a time period no more than about 3 hours, 2 hours, 1.5 hours, 1 hour, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, or less.

In certain embodiments, the various portions of the composition may include multiple drugs, such as carbidopa and levodopa, and their respective prodrugs. The relative proportions of the different drugs or prodrugs may vary at boundaries between the various portions (*i.e.*, different portions may have uniform drug ratios that differ from neighboring components), or may be formulated to change gradually over one or more portions of the composition.

In certain embodiments, the ratio of drug to prodrug (*e.g.*, carbidopa v. carbidopa prodrug; levodopa v. levodopa prodrug, *etc.*) may vary, depending on one or more factors such as relative solubility or other pharmacokinetic properties (*e.g.*, absorption, distribution, metabolism and excretion, *etc.*).

Another aspect of the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient; and (3) a substantially ascending release portion comprising

levodopa or a metabolic precursor thereof, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

Another aspect of the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient; and (3) a substantially elevating release portion comprising levodopa or a metabolic precursor thereof, formulated to elevate the substantially zero-order release rate to a higher level beginning at a predetermined time point.

Another aspect of the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a sleep-inducing agent; and, (2) a decarboxylase enzyme inhibitor formulated to provide an effective plasma concentration at a predetermined time after the administration of the pharmaceutical composition to the patient.

In certain embodiments, the sleep-inducing agent is benzodiazepine (*e.g.*, LIBRIUM®, VALIUM®), a prescription sleeping aid medicine (*e.g.*, AMBIEN®, RESTORIL®, DESYREL®, and SONATA®), eszopiclone (*e.g.*, LUNESTA™), or a non-prescription (over-the-counter) sleeping aid medicine (*e.g.*, TYLENOL® PM, EXCEDRIN PM®, UNISOM® / NYTOL® / SLEEPINAL®).

In certain embodiments, the pharmaceutical composition is for administration to a patient before sleeping.

In certain embodiments, the pharmaceutical composition is for administration to a patient before sleeping, and the beginning of the delayed immediate release is calculated to begin just prior to the waking of the patient.

In certain embodiments, the pharmaceutical composition further comprises: (3) a first delayed immediate-release (DIR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of the predetermined time.

In certain embodiments, the pharmaceutical composition further comprises: (4) a second delayed controlled release (DCR) portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period after the predetermined time, to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the predetermined time after administration is 6 to 9 hours after administration.

In certain embodiments, the rapid drop of levodopa takes place in less than two hours.

In certain embodiments, the formulation further comprises one or more of a dopamine precursor, such as L-dopa; a dopaminergic agent, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a dopaminergic and anti-cholinergic agent, such as amantadine (SYMMETRYL®, SYMADINE®); an anti-cholinergic agent, such as trihexyphenidyl (ARTANE®), benztropine (COGENTIN®), ethopropazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopamine agonist, such as apomorphine, bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), lisuride (DOPERGINE®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a MAO-B (monoamine oxidase B) inhibitor, such as selegiline or deprenyl (ATAPRYL®, CARBEX®, ELDEPRYL®); a COMT (catechol O-methyltransferase) inhibitor such as CGP-28014, entacapone (COMTAN®), or tolcapone (TASMAR®); a muscle relaxant, such as baclofen (LIORESAL®); a sedative, such as Clonazepam (RIVOTRIL®); an anticonvulsant agent, such as carbamazepine (TEGRETOL®); a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®); a dopamine blocker, such as haloperidol (HALDOL®); a β-blocker, such as propranolol (INDERAL®, INDERAL-LA®); a carbonic anhydrase inhibitor, such as acetalzolamide (DIAMOX®) or methazolamide (NEPTAZANE®); a narcotic agent, such as codeine (TYLENOL # 3®); a GABAergic agent, such as gabapentin (NEURONTIN®); or an alpha antagonist, such as clonidine (CATAPRESS®).

In certain embodiments, the formulation further comprises a stool softener selected from: bran or psyllium (*e.g.*, Metamucil, Fiberall), methylcellulose (*e.g.*, Citrucel), polycarbophil, docusate (*e.g.*, Colace, Surfak), docusate sodium and casanthranol combination (*e.g.*, Peri-Colace, Diocto C, Silace-C), magnesium hydroxide (*e.g.*, Phillips' Milk of Magnesia), magnesium citrate, sorbitol, polyethylene glycol solution (*e.g.*,

MiraLax), lactulose (*e.g.*, Cephulac, Cholac, Constilac), lubiprostone (*e.g.*, Amitiza) or other osmotic or stimulant laxatives (*e.g.*, Bisacodyl, Cascara, Castor oil, Senna, Tegaserod / Zelnorm), and natural stool softeners.

Alternatively, the stool softener(s) may be separately administered. For example, the stool softener(s) may be administered at a time when the effective compositions of first IR portion, the second substantially zero order release portion, or the substantially ascending release portion (such as the second IR portion) are being released.

Particular such embodiments provide a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient in less than about 2 hours of administration to the patient; and, (2) a second substantially zero order release portion comprising levodopa or the precursor, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa or the precursor in the patient; wherein at least the first IR portion further comprises a decarboxylase enzyme inhibitor, and the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

In certain embodiments, the ratio of the decarboxylase inhibitor to levodopa or its precursor in the first IR portion is about 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, or greater. The ratio may be different in different portions or sub-portions. For example, in the second sustained release portion, two or more sub-portions may be present, each having a different inhibitor / levodopa ratio. In certain embodiments, the ratio for the sub-portions to be released first (earlier) may be higher than that for the sub-portions to be released last (later).

In addition, the carbidopa and levodopa compositions may be released at different rates from different portions or sub-portions. For example, although the carbidopa / levodopa ratio may be consistently 1:4 in all subportions of the second substantially zero order release portion, the earlier sub-portions may release carbidopa faster, such that the release carbidopa / levodopa ratio is more than 1:4. Thus “release ratio” is defined as the ratio of two substances (*e.g.*, carbidopa and levodopa) released at a given time point.

In certain embodiments, the pharmaceutical composition further comprises: (3) a substantially ascending release portion (such as the second IR portion) comprising levodopa or the precursor, formulated to effect a rapid drop of levodopa concentration in the patient

to below the therapeutically effective concentration at the end of the treatment period.

In a related embodiment, the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient within about 2 hours of administration to the patient; (2) a second substantially zero order release portion comprising levodopa or the precursor, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa or the precursor in the patient; and (3) a substantially ascending release portion comprising levodopa or the precursor, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

In certain embodiments, the levodopa concentration in the patient drops below the therapeutically effective concentration at the end of the treatment period within about 2 hours, *e.g.*, within about 45 minutes, 1 hour, 1.5 hours, or 2 hours after the start of the substantially ascending release portion.

In certain embodiments, the levodopa precursor may be a methyl, ethyl, or propyl ester of levodopa, or a combination thereof. In certain embodiments, the levodopa precursor may be (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid, 3-hydroxy-L-tyrosine ethyl ester, phenylglycine, or a mixture thereof.

In certain embodiments, the ratio of the decarboxylase inhibitor to levodopa or the precursor in the first IR portion is about 1:3 or greater.

In certain embodiments, one or more of the various portions may comprise one or more additional drugs, such as the ones listed above.

In certain embodiments, the release ratio of the decarboxylase inhibitor to levodopa and/or its precursor varies between the start and the end of dispensing the second substantially zero order release portion.

In certain embodiments, the ratio changes substantially continuously over the release period of the second substantially zero order release portion.

In certain embodiments, the ratio is substantially constant during all or a part of the release period of the second substantially zero order release portion.

In certain embodiments, the substantially ascending release portion (such as the

second IR portion) comprises a decarboxylase enzyme inhibitor.

In certain such embodiments, the ratio of the inhibitor to levodopa and/or the precursor in the second IR portion is less than 1:4, such as 1:6, 1:8, 1:10, 1:15, 1:20, or less.

In certain embodiments, decarboxylase enzyme inhibitor is carbidopa, a carbidopa prodrug, benserazide, methylphenidate, or a combination thereof.

Unlike levodopa, carbidopa and benserazide are not pharmacologically / pharmacodynamically active, and they both have excellent toxicological profiles.

In certain embodiments, the total dose of the decarboxylase enzyme inhibitor per day per human patient is in the range of about 75 – 600 mg, or in the range of about 100 – 500 mg, or in the range of about 100 – 400 mg.

In certain embodiments, the total dose of levodopa and/or metabolic precursor thereof per day per human patient is between about 50 mg and about 300 mg.

In certain embodiments, at least one of the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) further comprises at least one dopamine transport inhibitor, preferably in sufficient amount to decrease dopamine elimination.

In certain embodiments, the dopamine transport inhibitor is methylphenidate.

In certain embodiments, the dopamine transport inhibitor is present in an amount of about 3 mg to about 60 mg.

In certain embodiments, the dopamine transport inhibitor is released starting after a delay of about 2 hours to about 7 hours.

In certain embodiments, the dopamine transport inhibitor is released over a period of time of about 1 hour to about 6 hours.

In certain embodiments, the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are formulated to provide a sustained dose over at least 4 hours, 6 hours, 7 hours, 8 hours, 12 hours, 16 hours, 20 hours, or 24 hours when administered to the patient.

In certain embodiments, the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are formulated into a stack of compressed inserts encased inside a shell or coating, each portion having an independent dissolution profile, wherein drug is released only from an exposed surface at a predetermined face of the stack, *e.g.*, through an

opening at one end of the shell (*e.g.*, the multilayered tablet).

In certain embodiments, some or all of the beads are coated by a dispersion-promoting coating, *e.g.*, exterior to a bioadhesive coating.

In certain embodiments, the beads are less than about 1 mm in diameter.

In certain embodiments, the beads are dispersed in a matrix that disintegrates in less than about 5 minutes, 4 min., 3 min., 2 min., or less than 1 min.

In certain embodiments, the beads are dispersed in an eroding tablet that gradually erodes over the treatment period.

In certain embodiments, the tablet is at least partially coated by a bioadhesive material and/or an immediate release portion.

In certain embodiments, the bioadhesive material, if present, is exposed upon dissolution of the immediate release portion.

In certain embodiments, the shell is fully or partially coated by a bioadhesive polymeric material.

In certain embodiments, the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are each formulated as a one or more, preferably a plurality of, individual beads, each of the portions having an independent dissolution profile (*e.g.*, the multiparticulate capsule).

In certain embodiments, the ratio of beads corresponding to the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (such as the second IR portion) (if present), are customized for the patient to provide a predetermined release profile, *e.g.*, to provide a predetermined duration of release, a predetermined rate of reaching a therapeutic plasma concentration of the drug or prodrug, or a predetermined maximum release rate (*e.g.*, customized for the size, sensitivity, or clearance rate of the particular patient), *etc.* For example, using more of the first IR portion may increase the rate at which a therapeutic plasma concentration is reached, using more of the second substantially zero order release portion may increase the maximum release rate and the sustained plasma concentration of the drug or prodrug, and using a different second substantially zero order release portion (or an additional sustained release portion) having additional reserves of drug or additional coatings to delay release can extend the duration of the sustained release phase.

In certain embodiments, some or all of the beads are fully or partially coated by a

bioadhesive polymeric material. For example, the beads in the first IR portion may not be coated, but the beads of the second (if present) and third portions (if present), may be so coated to assist delivery of drug over an extended period of time.

In certain embodiments, at least the substantially zero-order release rate second portion is coated or partially covered by a bioadhesive polymeric material.

In certain embodiments, the bioadhesive polymeric material is selected from polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric) anhydride), (need to make sure these are fixed throughout specification), blends, and copolymers thereof.

In certain embodiments, the bioadhesive polymeric material is poly(fumaric-co-sebacic) anhydride.

In certain embodiments, the bioadhesive polymeric material comprises a catechol moiety. For example, the bioadhesive polymeric material may comprise a mixture of a polymeric material and a compound comprising a catechol moiety selected from L-dopa, D-dopa, dopamine, or carbidopa. In addition, the bioadhesive polymeric material may be selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends and copolymers thereof.

In certain embodiments, the bioadhesive polymeric material is covalently functionalized with a catechol moiety, such as one derived from L-dopa, D-dopa, dopamine, or carbidopa.

In certain embodiments, the pharmaceutical composition is formulated for oral administration, or for parental administration.

In certain embodiments, the pharmaceutical composition is suitable for human administration, or for veterinary treatment of a non-human mammal.

In certain embodiments, the pharmaceutical composition is provided in solid forms (*e.g.*, powders, beads, *etc.*). In other embodiments, certain portions or the whole pharmaceutical composition are in liquid forms. For example, the IR portion may be in the

form of a liquid, while the CR (second) portion or sub-portions may be suspended as tiny particles or beads in the liquid IR. Alternatively, an inert pharmaceutically acceptable material, carrier, or excipient may be liquid, while both the IR and the CR may be suspended as tiny particles or beads in the liquid.

In certain embodiments, at least one adverse side effect (*e.g.*, the on-off effect or the the wearing off effect, *etc.*) associated with the treatment of a patient suffering from Parkinson's disease and/or another movement disorder is reduced or eliminated.

In certain embodiments, the subject pharmaceutical composition provides a substantially reduced degree of fluctuation in the plasma levels of the effective ingredients (*e.g.*, levodopa or carbidopa) compared to an immediate release pharmaceutical composition of the same dose administered three times daily.

Another aspect of the invention provides a method of making a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising combining the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (such as the second IR portion) (if present), of any of the subject pharmaceutical composition into a single dosage form.

Another aspect of the invention provides a method of treating a patient suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient any of the subject pharmaceutical compositions discussed herein.

In certain embodiments, the method comprises first administering to the patient the subject pharmaceutical composition with the first IR portion and the second zero-order release portion, followed by administering the substantially ascending release portion when the previously administered pharmaceutical composition is or is about to be completed in the patient.

Another aspect of the invention provides a packaged pharmaceutical preparation comprising the subject pharmaceutical composition, in an amount sufficient to treat a patient suffering from Parkinson's disease or another movement disorder, a pharmaceutically acceptable carrier, and a label or instructions (written and/or pictorial) for the use of the formulation for treating Parkinson's disease or another movement disorder, wherein the pharmaceutical composition is formulated to provide a sustained and/or increasing dose over at least about 6, 7, 8, 10, 12, 14, 16, 18, 20, or more hours when administered to the patient.

Another aspect of the invention provides a pharmaceutical preparation comprising the subject pharmaceutical composition, provided in the form of a transdermal patch and formulated for sustained release of the pharmaceutical composition in order to administer an amount sufficient to treat a patient suffering from Parkinson's disease and/or another movement disorder, wherein the pharmaceutical composition is formulated to provide a sustained substantial zero-order release over at least about 6, 7, 8, 9, 10, 12, 14, 16, 18, 20 or more hours when the patch is applied to the patient.

Another aspect of the invention provides a single dosage formulation for treatment of a movement disorder comprising levodopa or a metabolic precursor thereof, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 7, 8, 9, 10, 12, 14, 16, 18, 20 or more hours.

In certain embodiments, the single dosage formulation further comprises a decarboxylase enzyme inhibitor.

In certain embodiments, the single dosage formulation includes a first immediate-release (IR) portion to attain a therapeutically effective concentration of the levodopa or precursor with about 2 hours (*e.g.*, about 1.5 hrs, 1 hour, 45 min., 30 min., 20 min., 15 min., 10 min., 5 min., 2 min., 1 min., *etc.*) of administration to a patient. In certain embodiments, the single dosage formulation may further comprises: (1) a sustained zero-order release portion to maintain the therapeutically effective concentration of levodopa over a first period of hours; and, (2) a substantially ascending-release portion to maintain the therapeutically effective concentration of levodopa at the end of the sustained zero-order release portion; wherein the single dosage formulation, upon administration to the patient, produces a therapeutically effective concentration of the levodopa or precursor with about 2 hours (*e.g.*, less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration to a patient.

In certain embodiments, the ascending release portion provides for a rate of decrease of levodopa in the patient from a therapeutically effective concentration to a sub-therapeutically effective concentration (*e.g.*, < 75%, 50%, 25% or less) in a second period of time less than about 2 hours, *e.g.*, within about 45 minutes, 1 hour, 1.5 hours, or 2 hours, *e.g.*, to reduce sleep side effects.

In certain embodiments, the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

In certain embodiments, the decarboxylase enzyme inhibitor is present in only the first IR portion and the sustained zero-order release portion.

In certain embodiments, the decarboxylase enzyme inhibitor is present in all the portions, wherein the ratio of decarboxylase enzyme inhibitor to levodopa is different amongst different portions, *e.g.*, the ratio is higher in earlier-released portions than in later-released portions.

In certain embodiments, the sustained zero-order release portion comprises two or more sub-portions differing in the ratio of decarboxylase enzyme inhibitor to levodopa, *e.g.*, the ratio is higher in earlier-released portions than in later-released portions.

In certain embodiments, at least one of the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion further comprise at least one dopamine transport inhibitor, preferably in sufficient amount to decrease dopamine elimination.

In certain embodiments, the second substantially zero order release portion, and/or the substantially ascending release portion further comprise a bioadhesive polymeric material.

In certain embodiments, the the bioadhesive polymeric material comprises an additive that stabilizes the polymeric material from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive polymeric material comprises an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

Another aspect of the invention provides a single dosage formulation for treatment (*e.g.*, once-a-day) of a movement disorder comprising levodopa or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor, wherein the single dosage formulation, upon administration to the patient, produces a therapeutically effective concentration of the levodopa or precursor with about 2 hours (*e.g.*, in less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration to a patient, the therapeutically effective concentration being

maintained for a period of hours, then at the end of the dosing decreases to a sub-therapeutically effective concentration to, for example, reduce sleep side effects, in a period of time less than about 2 hours, *e.g.*, within about 45 minutes, 1 hour, 1.5 hours, or 2 hours.

Another aspect of the invention provides a therapeutic composition as described above, except that the dosage form is coated by a layer of delayed-release coating, such that the first IR portion will not start to be released until after a pre-determined period of time, such as the normal 6-10 hours of sleep time. According to this embodiment, a dose taken by the patient at night, for example, just before sleep, would start to be released and thus become effective just before or around the time the patient wakes up in the morning. This would allow the patient to have an effective plasma concentration of levodopa or precursor thereof upon waking in the morning, and the patient can immediately participate in normal daily activities without delay.

An additional advantage of the subject formulation relates to tolerance. Specifically, with enteral infusion, patients generally develop tolerance after prolonged period of treatment. However, the subject formulation has the added benefit of having a "break" during the night, so tolerance is generally not developed.

In a related aspect, the invention provides a general method of delivering a pharmaceutical composition, comprising administering to an individual the pharmaceutical composition coated by a delayed release coating, such that the release of the effective components of the pharmaceutical composition is delayed by a predetermined period of time, *e.g.*, at least about 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, or more.

In a related aspect, the invention provide a pharmaceutical composition coated by a delayed release coating, such that upon administering the pharmaceutical composition to an individual, the release of the effective components of the pharmaceutical composition is delayed by a predetermined period of time, *e.g.*, at least about 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, or more.

In certain embodiments, the pharmaceutical composition is administered at night, such that the delayed release starts the next morning.

In certain embodiments, the pharmaceutical composition with the delayed release coating is administered with the same pharmaceutical composition without the delayed release coating, such that the individual needs only take medicine once rather than twice (or multiple times) a day.

Another aspect of the invention provides a packaged pharmaceutical composition for

the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first pharmaceutical composition comprising the subject pharmaceutical composition for day time administration (*e.g.,* need not have sleep0inducing agent); (2) a second pharmaceutical composition comprising the subject pharmaceutical composition for night time administration (*e.g.,* comprising sleep-inducing agent).

In certain embodiments, the first and/or the second pharmaceutical composition is packaged separately as individual doses.

In certain embodiments, the the package comprises at least one dose each of the first and the second pharmaceutical compositions.

In certain embodiments, the first and the second pharmaceutical compositions are distinctively marked by color, shape, and/or size.

In certain embodiments, the packaged pharmaceutical composition further comprises an instruction that instructs a patient to take the first pharmaceutical composition as a day dose, and to take the second pharmaceutical composition as a night dose.

In certain embodiments, the package comprises sufficient doses for treating a patient over a week, 2 weeks, a month, 3 months, 6 month or more.

Another aspect of the invention provides drug delivery devices, such as those described herein below (*e.g.*, those in Figures 1-14 and 18-42, and those described in the Examples. Effective compositions (drugs and/or prodrugs, *etc.*) in these devices may be formulated to achieve any desired release profiles. In the case of levodopa / carbidopa delivery, for example, these devices may be used to achieve the subject drug release profiles, such as those depicted in Figures 15 and 16. Typically, it is desired that the patient's plasma levels of levodopa are within a therapeutic window, *e.g.*, between about 680 and 3400 ng/mL, during periods of activity, *e.g.*, during most or all waking hours. Preferably, administration of a composition of the invention does not provide a plasma level of levodopa above 3400 ng/mL at any time during the course of administration.

Thus, one aspect of the invention provides a multiparticulate pharmaceutical composition, comprising: (1) a plurality of pellets, each said pellets comprising a core comprising one or more effective ingredients; and (2) a matrix material; wherein the pellets are dispersed in the matrix material, and are released upon dissolution of the matrix material.

In certain embodiments, the matrix material disintegrates within about 5 minutes, 4 min., 3 min., 2 min., or less than 1 minute in an aqueous solution.

In certain embodiments, the aqueous solution is gastric acid.

In certain embodiments, the matrix material comprises a cushioning material.

In certain embodiments, the pharmaceutical composition is an eroding tablet and the matrix material gradually erodes over a predetermined period of time.

In certain embodiments, the eroding tablet is at least partially coated by a support material or a bioadhesive material.

In certain embodiments, the plurality of pellets comprise two or more different types of pellets.

In certain embodiments, a first type of pellets further comprises one or more coatings around the core of each pellet.

In certain embodiments, the coatings comprise a bioadhesive polymer, a composition for controlled release, and a dispersion-promoting composition.

In certain embodiments, the coatings comprise a bioadhesive polymer, a composition for controlled release, a composition for delayed release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

In certain embodiments, the different coatings, if present, are in two or more discrete layers.

In certain embodiments, at least two different coatings, *e.g.*, a bioadhesive polymeric material and a controlled-release composition, are combined in the same coating layer.

In certain embodiments, the layers comprise a controlled-release layer disposed around the core, a bioadhesive polymeric material layer disposed around the controlled-release layer, and a dispersion-promoting layer disposed around the bioadhesive polymeric material layer.

In certain embodiments, the effective ingredients comprise about 50-80% (v/v) of the coated pellets.

In certain embodiments, the effective ingredients are at least about 60% (v/v) of the coated pellets, and the effective ingredients are cohesive, plastic, and engage in hydrogen bonding.

In certain embodiments, the pellets are no more than 3 mm, 2 mm, 1 mm, 0.8 mm, 0.7 mm, 0.5 mm, 0.3 mm, or 0.1 mm in size.

In certain embodiments, the pellets are substantially homogeneous in size and/or shape.

In certain embodiments, the core is substantially free of microcrystalline cellulose.

In certain embodiments, the effective ingredient is one or more of: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane, sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine, domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycine, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam, ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts thereof.

Another aspect of the invention provides method to formulate a pharmaceutical composition, comprising: (1) blending the pharmaceutical composition to form a dry mix; (2) granulating the dry mix under low shear condition with a granulation fluid to form a wet granulation; (3) extruding the wet granulation through a screen-type extruder to form extrudate; (4) spheronizing the extrudate to form spheronized pellets; and (5) drying the pellets.

In certain embodiments, the pharmaceutical composition comprises two or more effective ingredients.

Another aspect of the invention provides method to formulate a pharmaceutical composition, comprising: (1) blending the pharmaceutical composition to form a dry mix; (2) granulating the dry mix under

In certain embodiments, the eroding tablet is at least partially coated by a support material or a bioadhesive material.

Another aspect of the invention provides a pharmaceutical composition formulated by any of the subject methods.

Another aspect of the invention provides a method to formulate a pharmaceutical composition, comprising: (1) blending the pharmaceutical composition to form a dry mix; (2) granulating the dry mix under low shear condition with a granulation fluid to form a wet granulation; (3) drying the wet granulation to form dried granulation; (4) grinding the dried granulation, and sieving through a screen of predetermined size to form sieved granules; (5) blending in a lubricant to the sieved granules to form a uniformly lubricated dry mix.

In certain embodiments, the the pharmaceutical composition comprises two or more effective ingredients.

In certain embodiments, the the effective ingredients comprise levodopa and/or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor.

In certain embodiments, the pharmaceutical composition comprises a bioadhesive polymeric material and/or a pharmaceutically acceptable excipient.

In certain embodiments, the pharmaceutical composition is substantially free of microcrystalline cellulose.

In certain embodiments, in step (1), the pharmaceutical composition is substantially free of lubricants.

In certain embodiments, the granulation fluid is purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone.

In certain embodiments, the method further comprises: passing the lubricated dry mix through a second screen.

In certain embodiments, the method further comprises: compressing the lubricated dry mix into a tablet.

In certain embodiments, the method further comprises: film-coating the tablet with one or more coating compositions.

In certain embodiments, the coating compositions comprise a bioadhesive polymeric material, a composition for controlled-release, a composition for delayed-release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

In certain embodiments, the different coating compositions, if present, are in discrete layers.

In certain embodiments, at least two different coating compositions are mixed in the same coating layer.

Another aspect of the invention provides a pharmaceutical composition formulated with the subject methods.

Another aspect of the invention provides a multiparticulate pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first immediate-release (IR) portion comprising: (a) a

plurality of pellets comprising levodopa or a metabolic precursor thereof (levodopa pellets), and (b) a plurality of pellets comprising carbidopa or a prodrug thereof (carbidopa pellets), wherein said first IR portion is formulated to provide a therapeutically effective concentration of levodopa in the patient within about 30 minutes of administration to the patient, and (2) a second portion comprising a plurality of pellets (levodopa-carbidopa pellets), each comprising: (a) a first core comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof); and (b) a bioadhesive polymeric material coating the first core, wherein said second portion is formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the w/w ratio of carbidopa: levodopa is about 1:4 in the first and second portions.

In certain embodiments, the second portion comprises about 80-90% of the levodopa in the pharmaceutical composition.

In certain embodiments, the pharmaceutical composition further comprises: (3) a third portion comprising a plurality of pellets (levodopa-bioadhesive pellets), each comprising: (a) a second core comprising levodopa (or a metabolic precursor thereof); and, (b) a bioadhesive polymeric material coating the second core, wherein the second and third portions are formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the second and third portions comprise about 80-90% of the levodopa in the pharmaceutical composition.

In certain embodiments, the second portion comprises about 60-70% of the levodopa in the pharmaceutical composition.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all disposed in a capsule.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all dispersed in a matrix material that disintegrates within about 5 minutes in an aqueous solution.

In certain embodiments, the matrix material comprises a cushioning material, *e.g.*, for absorbing shocks and/or reducing frictions on the surface of the coated pellets.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-

carbidopa pellets, and the levodopa-bioadhesive pellets are all dispersed in a matrix of an eroding tablet that gradually erodes over a predetermined period of time.

In certain embodiments, the eroding tablet is at least partially coated by a support material or a bioadhesive material.

In certain embodiments, the bioadhesive polymeric material coating the first and the second cores further comprises a dispersion-promoting agent, such as hydroxypropylcellulose.

In certain embodiments, the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets (if present) are no more than about 2 mm, 1 mm, 0.8 mm, 0.7 mm, 0.5 mm, 0.3 mm, or 0.1 mm in size.

In certain embodiments, the pellets are substantially homogeneous in size and/or shape.

In certain embodiments, the pharmaceutical composition is substantially free of microcrystalline cellulose.

In certain embodiments, the bioadhesive material comprises an additive that stabilizes the material from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

In certain embodiments, the bioadhesive material comprises an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

Another aspect of the invention provides a multilayer tablet pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a first controlled-release (CR) layer comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the CR layer; (2) a second, bioadhesive layer covering at least a portion of the first CR layer; wherein the tablet is formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

In certain embodiments, the multilayer tablet pharmaceutical composition further comprises: (3) a third, immediate-release (IR) layer comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), said third layer covering at least a portion of the first CR layer and/or the second bioadhesive layer, wherein the w/w ratio of

carbidopa : levodopa is about 1:4 in the third IR layer.

In certain embodiments, the CR layer comprises about 75-85%, or about 80% of the total levodopa in the composition.

In certain embodiments, the subject multilayer tablet pharmaceutical composition further comprises: (4) a fourth, pre-compressed immediate-release (IR) portion comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), wherein said fourth portion is disposed within the CR layer, and wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the fourth portion.

In certain embodiments, the fourth portion comprises about 15-25% of the total levodopa in the composition, and the CR layer comprises about 50-70% of the total levodopa in the composition.

Embodiments described herein are contemplated to be combined with each other embodiments as appropriate. Embodiments described in detail under one aspect of the invention may be equally applicable for the other aspects of the invention.

Brief Description of the Drawings:

Figure 1 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. Layers **11-13** represent the immediate-release composition layer (IR), the substantially zero-order release rate composition layer, and the optional ascending release (*e.g.*, second IR) layer, respectively. Layer **14** is an insoluble plug that seals off one end of the open-ended container / shell **15**. In this embodiment, Layers **11, 12,** (and optionally **13**) are exposed and released in sequential order.

Figure 2 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. Beads **21-23** represents the immediate-release composition portion (IR), the substantially zero-order release rate composition portion, and the optional ascending release portion (such as the second IR portion), respectively. The container / shell encompassing the beads may be made from any pharmaceutically acceptable material, such as gelatin, starch, HPMC (hydroxypropyl methylcellulose), pullulan, and fast dissolving capsules. The concentric rings on the beads represent different layers of coating, each of which layers may have different compositions and/or result in different release profiles.

Figure 3 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three layers represents the immediate-release

composition layer (IR) **31**, a bioadhesive layer (hatched lines) **32**, and the substantially zero-order release rate composition layer **33**. There may be one or more well-defined exit ports **34** on the bioadhesive layer to allow the inner contents to be released, or the bioadhesive layer **32** may be permeable to release of the encapsulated drug. The port size may increase in diameter over time, or when the dissolution progresses.

Figure 4 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. It is essentially identical to that depicted in Figure 3 (*e.g.*, having IR layer **41**, bioadhesive coating **42**, zero-order release core **43**, and exit port **44**), with an additional (optional) core **45** inside the substantially zero-order release rate composition layer **43**, which optional core **45** is the ascending release layer (such as the second IR layer).

Figure 5 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three shown layers represent the immediate-release composition layer **(IR) 51**, and two substantially zero-order release rate composition layers (**CR1 52** and **CR2 53**). There may be more than two such substantially zero-order release rate composition layers, differing by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson disease therapeutic composition). The inner trilayer core is coated with a semi-permeable coating **54a**, which is then coated over by a bioadhesive layer or patch (hatched lines) **54b**. The therapeutic compositions are successively released through an orifice **56** close to the IR composition (proximal end) **51**. Optionally, the distal end of the shell may comprise a plug **55** that can push the therapeutic compositions towards the orifice **56** at the proximal end. The push mechanism can be any suitable means, such as a water-absorbing gel that swells when in contact with aqueous solution, or a gas-generating unit, or a rigid plate / plunger that can be driven by a micromotor (optionally externally activated).

Figure 6 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three shown cores represent the immediate-release composition core **(IR) 61**, and two substantially zero-order release rate composition cores (**CR1 62** and **CR2 63**), each coated by its own bioadhesive layer (hatched lines **620** and **630**, respectively). There may be more than two such substantially zero-order release rate composition cores, differing by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). All such cores are encased inside a shell **64** made from suitable materials such as gelatin.

Figure 7 is a schematic cross-section view (not to scale) of two embodiments of a portion of the dosage form (*e.g.*, the second zero-order release rate portion). In this specific example, the composition may be formed as a cylinder or a column, or have a trapezoid profile (right panel). The compositions (*e.g.*, levodopa **72** and carbidopa **71**) are released starting from the top face and progressing in the order shown by the arrow. The top (beginning) of the dosage form has a different carbidopa / levodopa ratio from the bottom (end) of the dosage form.

Figure 8 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The three shown layers represent the immediate-release composition core **(IR) 81**, one sub-portion of the substantially zero-order release rate composition **CR1 82**, and a second sub-portion of the substantially zero-order release rate composition **CR2 83**, in the form of beads with or without bioadhesive coating and/or delayed release coating, and a bioadhesive composition layer **84** adjacent to the zero-order release rate composition **CR1 82**. There can be more than one sub-portions of the substantially zero-order release rate composition embedded within layer **82** (such as **CR3**, **CR4**, *etc.*, not shown). Each sub-portion may differ by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). The different sub-portions may be coated with different delayed-release compositions (optionally with different thickness, *etc.*), and/or beads may adopt a patterned distribution within the **CR1** layer, such that the beads of the same sub-portion start to release therapeutic compositions at substantially the same time. Alternatively, beads of the same sub-portion may start to release therapeutic compositions at staggered time points to effect a specific release profile, such as an ascending release profile.

Figure 9 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The immediate-release composition layer **91** covers the bioadhesive composition layer **94**, which has a hollow core that may adopt any desired geometric shape (regular or irregular, symmetrical or asymmetrical). Once the IR layer **91** is dissolved, it exposes the peripheral ends of **CR1 93**. The bioadhesive layer **94** covers the inner contents, which are to be gradually released through the peripheral ends. In the shown embodiment, the center of the hollow core is occupied by a sub-portion of the zero-order release rate composition **CR2 92** (or the second IR release portion). The rest of the core is filled with other sub-portion(s) of the zero-order release rate composition **CR1 93**. The geometric shape allows gradually increasing (as shown) or decreasing (not shown)

amounts of drugs to be released in unit time periods. Each sub-portion may differ by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). The IR layer **91** can also be part of the **CR1 93** core, in form of a lip or lid (not shown).

Figure 10 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. In this shown embodiment, the device is shaped like a torus or donut with a central hole. The immediate-release composition layer **1001** covers the entire surface, or almost the entire surface of the device. Underneath the IR layer **1001** is the bioadhesive composition layer **1004**, which covers almost the entire surface except a portion of the inner surface of the donut hole. The inner core covered by the bioadhesive layer is one or more sub-portions of the zero-order release rate composition, for example, **CR1 1002** and/or **CR2 1003** as shown (or the second IR release portion). When the IR layer is dissolved, the inner surface of the donut hole not covered by the bioadhesive layer is exposed, creating an exit hole to allow the CR sub-portions to be released from the inner core of the device. Although shown as regularly-shaped in the figure, the CR inner cores need not be of regular and/or symmetric shape. Neither does the two or more CR sub-portions need to be horizontally arranged to effect simultaneous release. A vertical arrangement of the CR sub-portions within the inner core may be used to effect sequential release of different CR sub-portions.

Figure 11 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. The immediate-release composition **1101** covers the two ends of a rod-shaped device (although the IR can cover the entire surface of the device, not shown). Towards the more central parts of the rod are several sub-portions of the zero-order release rate composition **CR1 1102**, separated from one another by other sub-portions of the zero-order release rate composition **CR2 1103**. The release of each **CR2 1103** is delayed temporarily by a ring of bioadhesive composition **1104**, and by the adjacent layers of **CR1 1102**. Upon the fast release of IR **1101**, followed by sustained controlled release of **CR1 1102**, the rod may break into two or more smaller rods / parts due to the dissolution of **CR1 1102** sub-portions. Depending on the spacing between adjacent **CR2 1103** sub-portions, one or more **CR2 1103** sub-portions may start to release from one side, or both sides of the sub-portion.

Figure 12 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device – a bioadhesive buccal patch or buccal tablet

attaching to a mucosa of the mouth **1201**. The immediate-release composition layer **1202** covers one sub-portion of the zero-order release rate composition **CR1 1203**, which covers another sub-portion of the zero-order release rate composition **CR2 1204** (or the second IR release portion). The whole device may be formulated as a multilaminate bioadhesive buccal patch or tablet attaching to a mucosa area of the mouth. Either or both CR layers may have their own bioadhesive layer or patch (not shown).

Figure 13 shows a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device – a dose sipping system. According to this embodiment, the therapeutic compositions are deposited in a straw plugged at one end by a porous plug **1303**. By dipping the plug end of the straw into a liquid (*e.g.*, a glass of water), and applying suction through the open end of the straw **1304**, the patient will receive the therapeutic composition in the solution taken through the straw. As shown, the immediate-release composition **1301** forms a matrix that contains one or more sub-portions of the substantially zero-order release rate composition **CR1** and/or **CR2 1302**, in the form of beads with or without bioadhesive coating and/or delayed release coating. There can be more than one sub-portion of the substantially zero-order release rate composition embedded within matrix **1301** (such as **CR3**, **CR4**, *etc.*, not shown). The sub-portions may differ by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson's disease therapeutic composition). If the sub-portion(s) of the substantially zero-order release rate composition (*e.g.*, **CR1 1302**) are coated by bioadhesive layers, such sub-portions may adhere to the GI track and release their contents according to the designed release profile. Alternatively, the IR portion may also be formulated as beads embedded with the other CR beads within an inert matrix.

Figure 14 shows a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device. According to this embodiment, the therapeutic compositions are encompassed within a shell with a cap **1404** and a body **1405**. The cap **1404** may be made of gelatin or other equivalent materials, while the body **1405** may be a bioadhesive layer itself, or a part of the gelatin body coated with a bioadhesive composition. Once the device is internalized by a patient and the gelatin cap **1404** is dissolved, the immediate-release composition **1401** will be exposed and quickly released. This in turn allows one or more sub-portions of the substantially zero-order release rate composition **CR1 1402** and/or **CR2 1403**, either in the form of beads embedded within an inert matrix (not shown), with or without bioadhesive coating and/or delayed release

coating, or in the form of successive layers. Although the cross-section is shown as a rectangle, it can be in any suitable shape (such as oval), and need not be symmetrical or regularly shaped.

Figure 15 is a schematic drawing showing plasma concentration profiles of levodopa and carbidopa for an exemplary levodopa-carbidopa dosage formulation: Immediate Release – Controlled Release – Delayed/Extended Release profile.

Figure 16 is a schematic drawing showing plasma concentration profiles of levodopa and carbidopa for an exemplary levodopa-carbidopa dosage formulation: Immediate Release – Controlled Release - Ascending Release profile.

Figure 17 illustrates a blister packaging of an exemplary levodopa-carbidopa dosage formulation for day and night administration, *e.g.*, during a period of one week (other packages with different treatment cycles, such as monthly package with multiple such weekly packages, are also contemplated, but not shown). The dosage forms for day and night administration can be differentiated by *e.g.*, color, and optionally by shape, *etc*. The ratio of levodopa and carbidopa in the exemplary dosage formulations may be different for day and night administrations. In addition, the release rate of levodopa and carbidopa in the exemplary dosage formulations may be different for day and night administrations.

Figure 18 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 19 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 20 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 21 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 22 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 23 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 24 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 25 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 26 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 27 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 28 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 29 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 30 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 31 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 32 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 33 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 34 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 35 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 36 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 37 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 38 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 39 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 40 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 41 is a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device.

Figure 42 is a schematic drawing (not to scale) illustrating a cross-sectional view of

one design of the subject delivery device.

Figure 43 shows *in vitro* dissolution profile of levodopa-carbidopa for SINEMET® 10-100 tablets in 0.1 N HCl.

Figure 44 shows *in vitro* dissolution profiles of levodopa and carbidopa for SINEMET® CR 50-200 tablets in 0.1 N HCl.

Figure 45 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for SINEMET® 10-100 tablets.

Figure 46 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for SINEMET® CR 50-200 tablets.

Figure 47 shows plasma concentration profiles of levodopa and carbidopa in fasted beagle dogs for SINEMET® CR 50-200 tablets.

Figure 48 shows *in vitro* dissolution profiles of levodopa and carbidopa for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets in 0.1 N HCl.

Figure 49 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets.

Figure 50 shows *in vitro* dissolution profiles of levodopa and carbidopa for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets in 0.1 N HCl.

Figure 51 shows plasma concentration profiles of levodopa and carbidopa in fed Beagle dogs for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets.

Figure 52 shows *in vitro* dissolution profiles of levodopa and carbidopa for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets in 0.1 N HCl.

Figure 53 shows plasma concentration profiles of levodopa and carbidopa in fed Beagle dogs for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets.

Figure 54 shows *in vitro* dissolution profiles of levodopa and carbidopa for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets with pre-compressed insert in 0.1 N HCl.

Figure 55 shows plasma concentration profiles of levodopa and carbidopa in fed Beagle dogs for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets with pre-compressed insert.

Figure 56 shows *in vitro* dissolution profiles of levodopa and carbidopa for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets with pre-compressed insert in 0.1 N HCl.

Figure 57 shows plasma concentration profiles of levodopa and carbidopa in fed

beagle dogs for bioadhesive levodopa-carbidopa 200 mg/50 mg trilayer tablets with pre-compressed insert.

Figure 58 shows *in vitro* dissolution profiles of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg triple pressed tablets in 0.1 N HCl.

Figure 59 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for levodopa-carbidopa 200 mg/50 mg triple pressed tablets.

Figure 60 shows *in vitro* dissolution profiles of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg quadrilayer tablets in 0.1 N HCl.

Figure 61 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for levodopa-carbidopa 200 mg/50 mg quadrilayer tablets.

Figure 62 shows plasma concentration profiles of levodopa and carbidopa in fasted beagle dogs for levodopa-carbidopa 200 mg/50 mg quadrilayer tablets.

Figure 63 shows *in vitro* dissolution profiles of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg quadrilayer tablets in 0.1 N HCl.

Figure 64 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for levodopa-carbidopa 200 mg/50 mg quadrilayer tablets.

Figure 65 shows plasma concentration profiles of levodopa and carbidopa in fasted beagle dogs for levodopa-carbidopa 200 mg/50 mg quadrilayer tablets.

Figure 66 shows *in vitro* dissolution profile of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg bioadhesive ER pellets in phosphate buffered saline (pH 4.5).

Figure 67 shows *in vitro* dissolution profile of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg rapidly disintegrating pelletized ER tablets in phosphate buffer (pH 4.5).

Figure 68 shows *in vitro* dissolution profile of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg bioadhesive extended release pellets in phosphate buffer (pH 4.5).

Figure 69 shows *in vitro* dissolution profile of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg slow eroding pelletized ER tablets in phosphate buffer (pH 4.5).

Figure 70 shows *in vitro* dissolution profiles of levodopa-cabidopa for SINEMET® 10-100 Tablets in 0.1N HCl.

Figure 71 shows *in vitro* dissolution profiles of levodopa-cabidopa for SINEMET® CR 50-200 Tablets in 0.1N HCl.

Figure 72 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for SINEMET® 10-100 Tablets.

Figure 73 shows plasma concentration profiles of levodopa and carbidopa in fed beagle dogs for SINEMET® CR 50-200 Tablets.

Figure 74 shows plasma concentration profiles of levodopa and carbidopa in fasted beagle dogs for SINEMET® CR 50-200 Tablets.

Figure 75 shows *in vitro* dissolution profiles of levodopa-cabidopa for levodopa-carbidopa 200 mg/50 mg multiparticulate capsules in 0.1N HCl.

Figure 76 shows plasma concentration profiles of levodopa and cabidopa in fed beagle dogs for levodopa-carbidopa 200 mg/50 mg capsules.

Figure 77 shows plasma concentration profiles of levodopa and cabidopa in fasted beagle dogs for levodopa-carbidopa 200 mg/50 mg capsules.

Figure 78 shows *in vitro* dissolution profile of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg multiparticulate capsules in 0.1N HCl.

Figure 79 shows plasma concentration profiles of levodopa and cabidopa in fed beagle dogs for levodopa-carbidopa 200 mg/50 mg capsules.

Figure 80 shows plasma concentration profiles of levodopa and cabidopa in fasted beagle dogs for levodopa-carbidopa 200 mg/50 mg capsules.

Figure 81 shows *in vitro* dissolution profile of levodopa-cabidopa for levodopa-carbidopa 200 mg/50 mg pellet capsules in 0.1N HCl.

Figure 82 shows *in vitro* dissolution profile of levodopa-cabidopa for levodopa-carbidopa 200 mg/50 mg pellet capsules in 0.1N HCl and PBS – pH 4.5.

Figure 83 shows *in vitro* dissolution profile levodopa-cabidopa for levodopa-carbidopa 200 mg/50 mg pellet capsules in 0.1N HCl.

Figure 84 shows *in vitro* dissolution profile of levodopa-cabidopa for levodopa-carbidopa 200 mg/20 mg pellets encapsulated in gelatin and PULLULAN capsules.

Figure 85 shows *in vitro* dissolution profile of levodopa for levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 86 shows *in vitro* dissolution profile of levodopa for levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 87 shows *in vitro* dissolution profile of levodopa for levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 88 shows *in vitro* dissolution profile of levodopa for levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 89 shows *in vitro* dissolution profile of carbidopa for carbidopa 200 mg

pellets encapsulated in gelatin capsules.

Figure 90 shows *in vitro* dissolution profile of levodopa for levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 91 shows *in vitro* dissolution profile of levodopa for immediate release levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 92 shows *in vitro* dissolution profile of levodopa for immediate release levodopa 200 mg pellets encapsulated in gelatin capsules.

Figure 93 shows *in vitro* dissolution profiles of levodopa and carbidopa for levodopa-carbidopa 200 mg/50 mg multiparticulate capsules in 0.1 N HCl.

Figure 94 shows plasma concentration profiles of levodopa in fed beagle dogs for SINEMET® CR 50-200 Tablets and levodopa-carbidopa 200 mg/50 mg multiparticulate capsules.

Figure 95 shows plasma concentration profiles of carbidopa in fed beagle dogs for SINEMET® CR 50-200 Tablets and levodopa-carbidopa 200 mg/50 mg multiparticulate capsules.

Figure 96 shows *in vitro* dissolution profiles of levodopa and carbidopa for SINEMET® CR 50-200 Tablets in 0.1 N HCl.

Figure 97 provides an exemplary scheme or drug cycle regarding the release of different components of the subject single dosage formulation.

Detailed Description of Invention:

I. *Overview*

In general, the present invention relates to the treatment of movement disorders, such as Parkinson's disease and other movement disorders. In certain embodiments, the invention relates to particular dosage forms that provide release profiles of the particular therapeutic compounds that are the most effective for the intended therapeutic use (*e.g.*, treatment of Parkinson's disease).

In one aspect, the present invention provides a dosage form and a method for administering a movement disorder pharmaceutical composition (*e.g.*, levodopa / carbidopa) in a once-a-day or more frequent regimen that ameliorates or overcomes symptoms of a movement disorder (*e.g.*, Parkinson's disease) in a patient.

In one embodiment, the single dosage formulation of the subject invention comprises levodopa or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor,

wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours or more. For example, in one embodiment, the pharmaceutical composition of the single dosage formulation may comprise: (1) a first immediate-release (IR) portion that provides a therapeutically effective concentration of a drug in the patient with about 2 hours (*e.g.*, about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*) of administration to the patient; (2) a second substantially zero order release portion comprising the drug, formulated to release the drug at a substantially zero-order release rate over a predetermined sustained treatment period to maintain the therapeutically effective concentration of drug in the patient.

The subject dosage formulation is advantageous for reducing the "wearing off" and the "on off" issues. SINEMET® CR (DuPont Pharma), a controlled release dosage form was designed to provide slow and simultaneous release of levodopa and carbidopa (U.S. Pat. No. 4,900,755). In certain embodiments, the subject dosage formulations provide a longer period of levodopa release within the therapeutically effective concentration than SINEMET® does.

Certain embodiments of the invention overcome the gastric emptying problem, resulting in considerably less fluctuation in levodopa plasma levels, which in turn ameliorates the "on-off" problem.

Prolonged suppression of disease manifestations with many traditional dosage forms is constrained by the mechanism of absorption of levodopa from the gastrointestinal tract. Levodopa is absorbed by the active transport mechanism for amino acids, which is most active in the duodenum region of the small intestine. Sustained release is therefore limited by the transit time of the dosage form through the stomach and duodenum which, though highly variable from individual to individual and dependent upon nutritional state, typically takes only about 3 to 4 hours. Levodopa released after the 3-4 hour therapeutic window has passed is not bioavailable. SINEMET® CR carbidopa-levodopa controlled release tablets have about 75% of the bioavailability of SINEMET® carbidopa-levodopa conventional release tablets. *Physicians Desk Reference*, p. 979, (54th edition, Medical Economics Co., publisher, 2000). Mean time to peak concentration in healthy elderly subjects was found to be two hours for controlled release carbidopa-levodopa, and only 0.5 hours for the conventional form (*Physicians Desk Ref.*, 47th Ed., p. 976, 1993).

Certain delayed release dosage forms of the invention possess a coating that dissolves slowly in gastrointestinal fluid. Release of the active component is delayed until dissolution of the coating allows gastrointestinal fluid to contact a core of the dosage form containing the drug. In combination with such coatings, the invention further provides certain bioadhesive polymer materials that help retain the pharmaceutical composition, such as one including levodopa, in the stomach of the patient. Thus, the period of release of the composition is timed to capitalize on the window of bioavailability. In other words, certain dosage forms of the invention overcome the gastric emptying problem, resulting in considerably less fluctuation in levodopa plasma levels, which in turn alleviates the "on-off" problem. This is a significant advantage for delivering drugs like levodopa that have a short absorption window.

Another advantage of certain embodiments of the invention is that a high concentration of levodopa in a patient's system, such as a "long tail" of levodopa concentration drop resulting from large doses of controlled release of levodopa / carbidopa at the end of the regimen, may be avoided by using a substantially ascending release portion, such as a second IR portion, in the dosage form released at the end of the treatment window, *e.g.*, as the effects of carbidopa administration are waning, such that at the end of the therapeutic regimen (*e.g.*, at the end of the day), the plasma level of levodopa quickly drops to below the effective level, so that the dosage form will not cause sleeping / resting problems for the patient.

Traditionally, in order to maintain a sufficient levodopa concentration at the end of the traditional release profile, a large dose of controlled release of levodopa / carbidopa has to be used at the end of the traditional regimen, resulting in a "long tail" of levodopa concentration drop long after the ending of the desired treatment period / cycle. This in turn causes sleeping / resting problems for the patient.

The subject release profile replaces the last segment of the traditional release profile with a last IR portion. According to the subject release profile, before the start of this last segment, effective concentration of carbidopa decreases / diminishes, allowing the body to metabolize levodopa faster and clearing it rapidly from the system. The presence of the last IR portion compensates for this more rapid processing, thus maintaining the effective levodopa concentration towards the end of the release profile. However, after the end of the desired treatment period / cycle (*e.g.*, end of the day), levodopa in the last IR portion is quickly consumed, leaving no undesirable long tail to interfere with the sleeping / resting of

the patient.

In certain embodiments, the subject pharmaceutical compositions are formulated to deliver rapidly upon administration an immediate-release (IR) dose, followed by a sustained release dose to maintain the effective therapeutic concentration, *e.g.*, over at least 4 hours, and more preferably over at least 5, 8, 10, 12, 14, or even 16 hours after administration.

In certain embodiments, an immediate release is followed by a substantially zero-order release rate, which is optionally further followed by a substantially ascending rate of drug release, or additional immediate release. The substantially ascending rate of drug release compensates for the drop off in effective levodopa concentration in the patient's system when the second portion of substantial zero-order release reaches the end of its release profile (see Figure 15 below; compare the tail-down of the center curve, the corresponding rise of the right-most curve around the same time, and the relative stable plateau represented by the solid curve). For example, if the patient takes the medicine upon arising in the morning, a subsequent ascending release dose (such as the second IR portion) taken separately at mealtime (*e.g.*, dinner) would provide the patient with additional needed therapeutic agent, if necessary, without having to resort to a second full-dose of drug for the same treatment period (*e.g.*, day). The ascending portion (such as the second IR portion) may also be built into the single dosage treatment medicine (dosage form) such that the patient need only administer treatment once a day in the morning.

Figure 15 shows an illustrative (non-limiting) release profile of the subject dosage form. According to Figure 15, the first IR portion (left-most sharp curve) allows a quick increase of levodopa concentration in a patient's system to within a therapeutically effective concentration range or window (the two dashed lines). This process should occur in less than about 2 hours (*e.g.*, about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hr, 1.5 hrs, 2 hrs, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administering the dosage form, depending on specific needs. As the concentration reaches its peak, or slightly before or after reaching the peak of the first IR portion release, the second sustained release portion begins to release (the middle dotted-curve in Figure 15), such that the total levodopa concentration is maintained within the therapeutic window. Certain fluctuation in concentration is tolerated, so long as the total concentration is not too high or too low to fall outside the effective therapeutic window.

The zero-order release from the second portion is expected to maintain the total

concentration within the therapeutic window for several hours, such as about 4, 5, 6, 7, 8, 9, 10 or more hours, until the net release into the patient's system is less than the net uptake/metabolism by the system including metabolic processes and other degradation processes. At that point, the total concentration of levodopa may start to drop (the point where the middle dotted-curve touching the plateau region of the thick solid curve). In the absence of an optional ascending release portion (either built in the single dosage treatment regimen or taken separately), the effective concentration will assume a long-tailed drop. But with the optional ascending release portion (either built in the single dosage treatment regimen or taken separately), the release profile can be modified. According to this embodiment, the plateau region of the solid curve is extended to a total period of beyond about 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 20 hours or more. Again, some concentration fluctuation is tolerable during this extended plateau period, so long as it falls within the effective therapeutic window.

In an alternative embodiment, the substantially ascending release portion may comprise levodopa, formulated to elevate the substantially zero-order release rate to a higher level, beginning around a predetermined time point, such as within ½, 1, 1.5, or 2 hours of noon (*e.g.*, about 4-6 hours after administration to the patient).

At the end of the ascending release portion (such as the second IR portion), the (total) concentration of levodopa may optionally be allowed to drop quickly, *e.g.*, within 30-120 minutes, such as within about 45 minutes, 1 hr, 1.5 hrs, or 2 hrs, to below a predetermined sub-therapeu-tically effective concentration through, for example, controlling the inhibitor / levodopa ratio.

As used herein, "sub-therapeutically effective concentration" refers to a value below the minimal effective concentration, such as less than about 75%, 50%, or about 25% of the minimal therapeutically effective concentration, which may vary depending on individual patients.

It should be noted that, although in Figure 15 the total concentration represented by the solid line is shown as gradually declining, it need not be the case according to the instant invention. So long as the solid curve is within the therapeutic effective concentration, slight fluctuations may be tolerable. The concentration towards the end of the regimen is not necessarily lower than that towards the beginning of the regimen.

Also note that the size of the plateau represented by the flat portion of the solid curve need not be limited to 4-12 hours as shown in the illustrative Figure 15.

In an alternative embodiment, the same therapeutic composition as described above may be coated by a layer of delayed-release coating, such that the first IR portion will not start to be released until after a pre-determined period of time, such as the normal 6-10 hours of sleep time. According to this embodiment, the medicine taken by the patient at night, for example, just before sleep, would start to be effective just before the patient wakes up in the morning. This would allow the patient to have an effective therapeutic concentration already in his system when he wakes up in the morning, and immediately participate in his normal daily activities without delay.

Thus the invention provides a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising: (1) a sleep-inducing agent; and, (2) a decarboxylase enzyme inhibitor formulated to reach and maintain an optimal plasma concentration at a predetermined time after the administration of the pharmaceutical composition to the patient.

The sleep-inducing agent is advantageous in that it helps to ensure relatively uniform timing between administration and release of the decarboxylase enzyme inhibitor. For example, without the sleep-inducing agent, certain patients may fall sleep quickly after taking the medicine with the decarboxylase enzyme inhibitor, while others may take hours before they finally fall asleep. Assuming the same amount actual sleeping time is needed for both types of patients (*e.g.*, 7-8 hrs), the level of decarboxylase enzyme inhibitor may reach the designed optimal level only in certain patients just before they wake up. In patients who take longer to fall asleep, the optimal level may have already passed when these patients wake up.

Using a formulation with a sleep-inducing agent, patients will awaken with an effective plasma level of decarboxylase inhibitor and can take a morning dose of levodopa and/or carbidopa (as described above) without having to wait for the decarboxylase enzyme inhibitor to reach an effective level before levodopa starts to take effect.

Alternatively, the pharmaceutical composition with sleeping-inducing agent and decarboxylase enzyme inhibitor may additionally comprise delayed-release IR and delayed CR portions. Specifically: (3) a first delayed immediate-release (DIR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of the predetermined time; and (4) a second delayed controlled release (DCR) portion comprising levodopa and/or its precursor, formulated to release levodopa and/or the precursor at a substantially zero-order

release rate over a sustained treatment period after the predetermined time, to maintain the therapeutically effective concentration of levodopa in the patient.

These pharmaceutical compositions, either with or without the levodopa/carbidopa compositions, are suitable for administration to a patient before sleeping. If the sleep-inducing agent and the decarboxylase enzyme inhibitor do not comprise the levodopa / carbidopa composition, the levodopa / carbidopa composition may be separately administered to the patient in the morning upon waking. In this case, the decarboxylase enzyme inhibitor is formulated to reach and maintain an optimal plasma concentration just at or just prior to the wake-up time, *e.g.*, the predetermined time is about the average sleeping time from the administration of the sleep-inducing agent, such as 7 hrs, 8 hrs, 9 hrs, *etc*. In this case, the sleep-inducing agent and the decarboxylase enzyme inhibitor may be a "night pill," while the levodopa / carbidopa extended releasecomposition may be a "morning pill." In PD patients, the sequence of administering the two types of pills (night pill and morning pill) is critical to achieving the optimal therapeutic effect. Both dosage forms may be packaged together, for example, as compliance promoting twin blister packages, making it convenient and clear to the patient about the order and timing of administration of the two types of doses. Optionally, the different dosage forms may be configured differently, *e.g.*, by the appearance of the dosages themselves, such as different colors and/or different shapes, sizes, *etc.*, or by labeling used in the packaging.

If the sleep-inducing agent/decarboxylase enzyme inhibitor formulation further comprises the levodopa / carbidopa composition, the levodopa / carbidopa composition is formulated as delayed release formulation, such that levodopa / carbidopa will start to be released just at or just prior to the patient waking up, obviating the need for a separate morning dosage form.

In certain embodiments, the sleep-inducing agent is benzodiazepine (*e.g.*, LIBRIUM®, VALIUM®, HALCION®), Secobarbital (SECONAL®), a prescription sleeping aid medicine (*e.g.*, AMBIEN®, RESTORIL®, DESYREL®, and SONATA®), eszopiclone (*e.g.*, LUNESTA™), or a non-prescription (over-the-counter) sleeping aid medicine (*e.g.*, TYLENOL® PM, EXCEDRIN PM®, UNISOM® / NYTOL® / SLEEPINAL®).

Figure 97 provides an exemplary scheme or drug cycle regarding the release of different components of the subject single dosage formulation. Depending on the specific embodiments involved, not all components are necessarily present. The timings of release are approximate and for illustration purposes only, and may not be to scale. A typical

patient for the purpose of this figure follows a routine of waking up around 7 am in the morning and going to sleep around 10-11 pm at night. Specifically, for each portion (*e.g.*, 1st IR, substantial zero-order release, substantial elevating zero-order release, 2nd IR, sleep-inducing agent & decarboxylase inhibitor, *etc.*), the closed circle indicates the approximate start of drug release, and the arrowhead indicates the approximate end or tailing off of the release. For components not starting at about the time of administration, a delayed-release coating may be present to effect the delay. The stool softener, COMT inhibitor, and/or dopamine transport inhibitor, and other auxillary drug components, *etc.*, if present, may be released at any time during the drug cycle, with any effective components (1st IR, substantial zero-order release, 2nd IR, *etc.*), either simultaneously or sequentially (hence the dashed line).

In one embodiment, a patient can take one AM dose per day, and continue indefinitely if desirable. Alternatively, the patient may take one AM dose when waking up, followed by one PM dose before sleeping, and continue this pattern indefinitely if desirable. The PM dose may contain a sleep-inducing agent & a decarboxylase enzyme inhibitor. In yet another embodiment, the patient may take one PM dose per day, and continue indefinitely if desired. In this embodiment, the PM dose also contains effective components (*e.g.*, carbidopa / levodopa) in delayed-release formulation, such that release profile similar to the left-hand side of Figure 97 (Day 1) is achieved for Day 2.

It should be understood that such release profiles may also be used to divide the different components into multiple dosage systems (such as a sleep aid, a night-time formulation, and a morning formulation, *etc.*), so long as the overall formulations are designed to release the drugs at or about the times indicated on the scheme.

In certain embodiments, the subject dosage form allows rapid release of drug (*e.g.*, levodopa) in the morning at a rate that results in rapid and reproducible onset of action, reduced frequency of administration, reduced severity of side effects (motor fluctuations). The onset of action may be effected at about 5 minutes, 10 minutes, 15 minutes after the administration, or about 30 minutes, or about 45 minutes, or about 1 hour after the administration of the pharmaceutical composition comprising an immediate-release composition.

In certain embodiments, the ratio of carbidopa (or other equivalent decarboxylase inhibitors) to levodopa is variable, between different individuals / patients, and/or between the different stages of release (*e.g.*, immediate-release vs. substantially zero-order release

vs. the optional substantially ascending / rapid rate of release), and/or within each stage of release (*e.g.*, within the zero-order release stage).

Depending on specific situations, the carbidopa : levodopa ratio may be about 1:20, 1:15, 1:10, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, or about 6:1 or more.

The usual daily therapeutic dose of carbidopa is approximately 75 mg per day, but carbidopa apparently fails to elicit adverse effects even at doses of 400 mg per day (Ahlskog, *Hosp. Form.*, **27**: 146, 1992). Thus the total daily dose of carbidopa may be anywhere below about 600 mg, 500 mg, or 400 mg.

For example, to effect a rapid rise of carbidopa concentration in a patient's system, a greater than 1:4 ratio of carbidopa:levodopa may be used (*e.g.*, greater than 1:3, 1:2, 1:1, 2:1, *etc.*). This helps ensure that peripheral decarboxylase activity is substantially inhibited in the treated individual, without regard to any individual differences in peripheral decarboxylase level and/or activity. In contrast, compared to the standard 1:4 ratio, the carbidopa : levodopa ratio may be very low in the second IR portion (*e.g.* less than about 1:10, 1:15, 1:20, *etc.*), or carbidopa may be omitted from this portion altogether, such that a rapid drop in effective levodopa can be effected towards the end of regimen, allowing the treated patient to sleep or rest normally without being substantially affected by the lingering effects of levodopa therapy that can disrupt normal sleep patterns.

In fact, in certain embodiments, the carbidopa : levodopa ratio may vary even within a single release stage. For example, during the substantially zero-order release stage, the ratio may be closer to 1:4 when entering this stage, and gradually decrease to 1:5, 1:6, 1:8, 1:9, 1:10, *etc.*, such that at the end of this stage, the ratio is substantially smaller than the starting ratio. This effect can be achieved using a number of approaches. For example, carbidopa and levodopa may be mixed together and spun in a container to create a gradient of inhibitor : drug. Alternatively, carbidopa and levodopa may occupy two sides of an imaginal tilted plane dissecting a cylindrical column, such that an increasing or decreasing proportion of the dissolving surface comprises the inhibitor carbidopa. In a related embodiment, the release rate remains constant for the levodopa composition, while the release rate gradually decreases for carbidopa (see **Figure 7**). Yet another alternative is to stack many layers, each with a unique carbidopa:levodopa ratio, *etc.* Obviously, using these methods, the ratio may remain constant for any desired period or periods of time during the stage.

In other embodiments, the invention provides a bioadhesive dosage form that

releases the drug at the target absorption site, and is less prone to gastric emptying, thus resulting in a more reproducible and consistent plasma level of levodopa, a drug with a narrow absorption window. In certain embodiments, the bioadhesive layer / patch is used in conjunction with the substantially zero-order release composition.

Another approach to achieving a constant dopamine level in the brain is to work at the level of brain biochemistry. Dopamine in the brain, whether released by a pre-synaptic neuron or supplied by the delivery of levodopa through the brain blood barrier, is removed from the junction by mechanisms of dopamine uptake to stop information transfer. Partial blocking of the dopamine uptake could result in more constant dopamine levels in the brain without the need to modify the levodopa profile in the blood. Methylphenidate, a relatively safe drug used to treat children suffering from Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD), is a dopamine transport inhibitor. Methylphenidate has been used with levodopa in Parkinson's disease patients, resulting, however, in severe dyskinesia and other motor effects of levodopa on the patients, especially when the two drugs are delivered together. Camicioli, *et al.* "Methylphenidate Increases the Motor Effects of L-Dopa in Parkinson's Disease: a Pilot Study," *Clin. Neuropharmacol.* **24(4)**: 208-213, 2001.

However, when dosages are properly calibrated, the detrimental results associated with the co-delivery of levodopa and at least one dopamine transport inhibitor can be avoided and beneficial results achieved. Delivery of dopamine transport inhibitors too early in the levodopa-in-blood release profile enhances the adverse motor effects caused by high levels of dopamine in the brain. However, by properly adjusting the levodopa dose and proper timing of the dopamine transport inhibitor to block the dopamine transporter, substantially constant levels of dopamine in the brain can be achieved. Preferably, the dopamine transport inhibitor is administered as the dopamine levels start to decrease.

During normal brain function, dopamine is released in the synapse by neuron cells and eliminated by transport proteins. Co-treatment with a drug that inhibits the transport protein allows the dopamine to reside longer in the brain, thereby making the effective drug troughs shallow. Additionally, the efficient use of the method lowers concentration peaks by lowering levodopa dosing levels. Proper timing of the co-treatment with the two drugs is essential. Administering the dopamine transport inhibitor too early may result in peaks of brain dopamine and problems of dyskinesia. Administering the dopamine transport inhibitor too late may result in too little advantage, because the dopamine levels in the brain will have

already been depleted by the normal elimination processes. Proper timing of the transport inhibitor delivery to slightly after the predicted peak in brain dopamine concentration and keeping the inhibitor in place for some time extends the time that effective concentrations of the dopamine are present in the brain. However, extending the time of the transport inhibition too long can have deleterious effects, since it may lead to too high a dopamine concentration as additional levodopa is administered.

Thus, in certain embodiments, the invention provides dosage forms comprising levodopa and at least one dopamine transport inhibitor. The administration of the dopamine transport inhibitor may be delayed such that release coincides with the time the dopamine concentration level starts to decrease. The dopamine transport inhibitor is a compound capable of delaying the dopamine transporter from removing dopamine from the brain. In other words, the dopamine transport inhibitor precludes or diminishes the removal rate of dopamine by the dopamine transporter, thereby prolonging a concentration of dopamine in the brain. Dopamine transporter inhibitors include, but are not limited to, methylphenidate. In the formulation of the invention, methylphenidate may be present in an amount about 1 mg to about 60 mg, preferably from 1 mg to about 15 mg, more preferably, from about 5 mg to about 10 mg, and most preferably methylphenidate may be present in an amount of about 10 mg per dose.

In certain embodiments, a levodopa metabolic precursor like the levodopa ethyl ester of U.S. Pat. No. 5,840,756 (incorporated herein by reference) may be substituted for some or all of the levodopa in the various embodiments of the invention. Typically, levodopa is present in an amount from about 50 mg to about 300 mg, preferably from about 100 mg to about 200 mg and, more preferably, levodopa is present in an amount of about 100 mg to about 150 mg per dose. The amount of levodopa may also be adjusted accordingly if any of the other formulations described below are adapted for use in the instant invention.

As discussed above, the timing of the administration of the individual ingredients of the composition of the invention is important to achieve the desired leveling of peaks and troughs of dopamine concentrations when treating Parkinson's disease. Generally, it is desirable to administer levodopa and, optionally, a decarboxylase enzyme inhibitor, prior to the administration of at least one dopamine transporter inhibitor. Alternatively, the levodopa, decarboxylase enzyme inhibitor, and dopamine transporter inhibitor of the composition may be administered concurrently as a unit dose or co-administered as several

doses. Each ingredient, however, may be formulated either as an immediate release formulation or sustained release formulation with or without a time delay. The ratio of each ingredient may also vary between the first (and second, if present) immediate-release and the substantially zero-order release dose.

In certain embodiments, levodopa may be administered as an immediate-release formulation or a sustained-release delivery formulation wherein the levodopa is released over about 1 to about 4 hours. The decarboxylase enzyme inhibitor may be dosed as an immediate-release drug delivery formulation or a sustained-release delivery formulation (with levodopa or independently) wherein the decarboxylase enzyme inhibitor is released over about 1 to about 4 hours. Typically, the dopamine transporter inhibitor is formulated as an immediate-release formulation which releases after about a 2-hour to about 7-hour delay, and preferably after about a 3- to about 5-hour delay. Alternatively, the dopamine transporter inhibitor may be formulated as a sustained-release delivery formulation which releases over one to six hours after about a 1- to about 7-hour delay.

In certain embodiments, the subject pharmaceutical composition is formulated for variable dosing, such as customized dosing for individual patients.

Another aspect of the invention provides a method for making the pharmaceutical compositions with one or more features as described above.

Another aspect of the invention provides a method for using the pharmaceutical compositions with one or more features as described above, in treating a movement disorder, such as Parkinson's disease.

Another aspect of the invention provides the use of a pharmaceutical composition with one or more features as described above in manufacturing medicaments for the treatment of a movement disorder, such as Parkinson's disease.

The subject preparations and methods can be used as part of the treatments for human and/or other animal subjects. In addition to humans, other animal subjects to which the invention is applicable extend to both domestic animals and livestock, raised either as laboratory animals, pets or zoo animals, or for commercial purposes. Examples are rodents such as mice, rats, hamsters, or rabbits; dogs; cats; cattle; horses; sheep; hogs; and goats.

In certain embodiments, the method includes administering, conjointly with the subject pharmaceutical composition, one or more of other therapeutic compositions useful for the treat-ment of diseases, for which levodopa/carbidopa or pramipexole is indicated for. For example, in the case of treating Parkinson's Disease and certain movement disorders,

levodopa/carbidopa or pramipexole may be co-administered with a dopamine precursor, a dopaminergic agent, a dopaminergic and anti-cholinergic agent, an anti-cholinergic agent, a dopamine agonist, a MAO-B (monoamine oxidase B) inhibitor, a COMT (catechol O-methyltransferase) inhibitor, a muscle relaxant, a sedative, an anticonvulsant agent, a dopamine reuptake inhibitor, a dopamine blocker, a β-blocker, a carbonic anhydrase inhibitor, a narcotic agent, a GABAergic agent, or an α antagonist.

In certain embodiments, the method includes administering, conjointly with the pharmaceutical composition, one or more of physical therapy, occupational therapy, or speech / language therapy.

An agent to be administered conjointly with a subject compound may be formulated together with a subject compound as a single pharmaceutical preparation, *e.g.*, as a pill or other medicament including both agents, or may be administered as a separate pharmaceutical preparation.

Another aspect of the invention provides a packaged pharmaceutical composition, comprising the subject pharmaceutical composition in an amount sufficient to treat or prevent a movement disorder in a patient, which may additionally include a pharmaceutically acceptable carrier, and instructions (written and/or pictorial) describing the use of the formulation for treating the patient, wherein the patient suffers from ataxia, corticobasal ganglionic degeneration (CBGD), dyskinesia, dystonia, tremors, hereditary spastic paraplegia, Huntington's disease, multiple system atrophy, myoclonus, Parkinson's disease, progressive supranuclear palsy, restless legs syndrome, Rett syndrome, spasticity, Sydenham's chorea, other choreas, athetosis, ballism, stereotypy, tardive dyskinesia/dystonia, tics, Tourette's syndrome, olivopontocerebellar atrophy (OPCA), diffuse Lewy body disease, hemibalismus, hemi-facial spasm, restless leg syndrome, Wilson's disease, stiff man syndrome, akinetic mutism, psychomotor retardation, painful legs moving toes syndrome, a gait disorder, a drug-induced movement disorder, or other movement disorder.

In certain preferred embodiments, the movement disorder is Parkinson's disease.

Certain general features of the invention are further elaborated in the sections below.

II. *Definitions*

For convenience, certain terms employed in the specification, examples, and appended claims are collected here. All other terms have their ordinary meanings as

understood by a skilled artisan.

As used herein, "about" means within the pharmaceutically acceptable limits found in the United States Pharmacopia (USP-NF 21), 2003 Annual Edition, or available at the USP website, for amount of active pharmaceutical ingredients. With respect to blood levels, "about" means within FDA acceptable guidelines.

The term "adrenergic" refers to neurotransmitters or neuromodulators chemically related to adrenaline (epinephrine) or to neurons which release such adrenergic mediators. Examples are dopamine, norepinephrine, and epinephrine. Such agents are also referred to as catecholamines, which are derived from the amino acid tyrosine.

As generally used herein "bioadhesives" or "bioadhesive materials" refer to naturally occurring polymers which are bioadhesive or naturally occurring or synthetic polymers, which have been modified or which have been blended with an additive, to have improved bioadhesion. As generally used herein, "modified" refers to monomers or polymers which have undergone a chemical reaction.

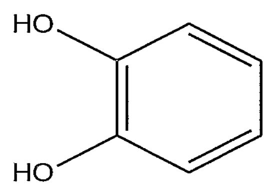
As used herein "bioadhesion" generally refers to the ability of a material to adhere to a biological surface for an extended period of time. Bioadhesion requires a contact between the bioadhesive material and a surface, for example, where the bioadhesive material penetrates into the crevice of the surface (*e.g.* tissue and/or mucus) and chemical bonds form. The amount of bioadhesive force is affected by both the nature of the bioadhesive material, such as a polymer, and the nature of the surrounding medium. Adhesion of materials to tissues may be achieved by (i) physical or mechanical bonds and/or (ii) secondary chemical bonds (*e.g.*, ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive interactions (*e.g.*, Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds and ionic bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are hydroxyl (-OH) and carboxylic acid groups (-COOH). Bioadhesive forces are measured in units of N/m^2. These forces are preferably determined by methods defined in U.S. Patent No. 6,197,346 to Mathiowitz *et al.* Bioadhesive forces, especially those exhibited by tablets, can also be measured using a Texture Analyser, such as the TA-TX2 Texture Analyser (Stable Micro Systems, Haslemer, Surrey, UK). As described by Michael J. Tobyn *et al* in *Eur. J. Pharm. Biopharm.*, 41(4):235-241 (1995), a mucoadhesive tablet is attached to a probe on the texture analyzer

and lowered until it contacts pig gastric tissue, which is attached to a tissue holder and exposed to liquid at 37 °C to simulate gastric medium. A force is applied for a set period of time and then the probe is lifted at a set rate. Area under the force/distance curve calculations are used to determine the work of adhesion. (See also Michael J. Tobyn *et al.*, *Eur. J. Pharm. Biopharm.*, 42(1):56-61 (1996) and David S. Jones, *et al.*, *International J. Pharmaceutics*, 151: 223-233 (1997)).

The term "biogenic amines" refers to a class of neurotransmitters which includes catecholamines (*e.g.*, dopamine, norepinephrine, and epinephrine) and serotonin.

As generally used herein "blend" refers to a mixture of two or more polymers or a mixture of one or more polymers with one or more low molecular weight additives containing a catechol functionality. The mixture can be homogeneous or heterogeneous.

As used herein "catechol" refers to a compound with a molecular formula of $C_6H_6O_2$ and the following structure:



Catechol

Bioadhesive materials contain a polymer with a catechol functionality or a polymer blended with catechol or a catechol derivative. For materials that contain polymers that have been modified with a catechol functionality, the molecular weight of the bioadhesive materials and percent substitution of the polymer with the aromatic compound may vary greatly. The degree of substitution varies based on the desired adhesive strength, it may be as low as 10%, 20%, 25%, 50%, or up to 100% substitution. On average at least 50% of the monomers in the polymeric backbone are substituted with at least one aromatic group. Preferably, 75-95% of the monomers in the backbone are substituted with at least one aromatic group or a side chain containing an aromatic group. In the preferred embodiment, on average 100% of the monomers in the polymeric backbone are substituted with at least one aromatic group or a side chain containing an aromatic group. The resulting bioadhesive material is a polymer with a molecular weight ranging from about 1 to 2,000 kDa, preferably 1 to 1,000 kDa, more preferably 10 to 1,000 kDa, most preferably 100 to 1,000 kDa. For materials in which a polymer has been blended with catechol or a catechol

derivative, the ratio of polymer to catechol can be varied in order to vary the bioadhesive properties of the material. The catechol or catechol derivative can be present in an amount from about 0.5% to about 95% by weight of the polymer, typically about 10% to about 75%, preferably about 10% to about 50% and more preferably about 10% to about 30%.

In certain embodiments of the invention, a polymer may be functionalized by covalently attaching catechol moieties or compounds comprising catechol moieties. Alternatively, a compound comprising a catechol moiety may be blended with a polymer to form a simple mixture with no covalent association between the catechol moieties and the polymer.

The term "catecholamines" refers to neurotransmitters that have a catechol ring (*e.g.*, a 3,4-dihydroxylated benzene ring). Examples are dopamine, norepinephrine, and epinephrine.

The term "cholinergic" refers to neurotransmitters or neuromodulators chemically related to choline or to neurons which release such cholinergic mediators.

The term "Degree of Fluctuation (DFL)" as used herein is expressed as :

$$DFL = (C_{max} - C_{min})/C_{avg}$$

produced by ingestion of the the composition of the invention or the t.i.d comparator.

The term "C_{max}" as used herein means maximum plasma concentration of pramipexole achieved by the ingestion of the composition of the invention or the t.i.d comparator. The term "C_{min}" as used herein means minimum plasma concentration of pramipexole achieved by the ingestion of the composition of the invention or the t.i.d comparator. The term "C_{avg}" as used herein means average plasma concentration of pramipexole achieved by the ingestion of the composition of the invention or the t.i.d comparator. C_{avg} is calculated by AUC over a 24 hours intervals divided by 24.

The term "T_{max}" as used herein means the time to achieve maximum plasma concentrations produced by ingestion of of the composition of the invention or the t.i.d comparator. The term "AUC" as used herein means the area under the plasma concentration-time curve, as calculated by the trapezoidal rule over the 24 hour interval for all the formulations.

As used in this application, the term "C_{min}" and "trough levels" should be considered synonyms. Likewise, "C_{max}" and "peak levels" should be considered synonyms.

The term "dopaminergic" refers to neurotransmitters or neuromodulators chemically

related to dopamine or to neurons which release such dopaminergic mediators.

The term “dopamine” refers to an adrenergic neurotransmitter, as is known in the art.

The term “ED_{50}” means the dose of a drug which produces 50% of its maximum response or effect.

An "effective amount" of, *e.g.*, a movement disorder pharmaceutical composition, with respect to the subject method of treatment, refers to an amount of the pharmaceutical composition in a preparation which, when applied as part of the subject dosage regimen brings about the desired correction / suppression of the movement disorder (*e.g.*, dyskinesis and/or bradykinesis) according to clinically acceptable standards.

The term “LD_{50}” means the dose of a drug which is lethal in 50% of test subjects.

The term "lethal therapeutic index" refers to the therapeutic index of a drug defined as LD_{50}/ED_{50}.

The term “metabolites” refers to active derivatives produced upon introduction of a compound into a biological milieu, such as a patient.

The term “orally deliverable” herein means suitable for oral, including peroral and intra-oral (*e.g.*, sublingual or buccal) administration, but tablets of the present invention are adapted primarily for peroral administration, *i.e.*, for swallowing, typically whole or broken, with the aid of water or other drinkable fluid.

A "patient," “individual,” or "subject" to be treated by the subject method can mean either a human or non-human animal.

The term “prevent,” “preventing,” or “prevention” as used herein means reducing the probability / risk of developing a condition in a subject (*e.g.*, a human), or delaying the onset of a condition in the subject, or lessening the severity of one or more symptoms of a condition (*e.g.*, a movement disorder) that may develop in the subject, or any combination thereof.

The term “prodrug” is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention. A common method for making a prodrug is to include selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations.

Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991).

The term "SeD_{50}" means the dose of a drug which is produces a particular side-effect in 50% of test subjects.

The term "side-effect therapeutic index" refers to the therapeutic index of a drug defined as SeD_{50}/ED_{50}.

A "subject" herein is an animal of any species, preferably mammalian, most preferably human. Conditions and disorders in a subject for which a particular agent is said herein to be "indicated" are not restricted to conditions and disorders for which the agent has been expressly approved by a regulatory authority, but also include other conditions and disorders known or believed by a physician to be amenable to treatment with the agent.

"Solid fraction" is the ratio of absolute to apparent density of a compact of the starch. A "compact" herein is a compressed tablet, prepared for example on a tablet press, consisting only of a sample of starch for which it is desired to measure tensile strength. A "solid fraction representative of the tablet" is a solid fraction selected to be similar to the solid fraction of tablets prepared according to the invention. Typically a solid fraction of about 0.75 to about 0.85, illustratively 0.8, will be selected.

The term "statistically significant" as used herein means that the obtained results are not likely to be due to chance fluctuations at the specified level of probability. The two most commonly specified levels of significance are 0.05 (p=0.05) and 0.01 (p=0.01). The level of significance equal to 0.05 and 0.01 means that the probability of error is 5 out of 100 and 1 out of 100, respectively.

By "transdermal patch" is meant a system capable of delivery of a drug to a patient via the skin, or any suitable external surface, including mucosal membranes, such as those found inside the mouth. Such delivery systems generally comprise a flexible backing, an adhesive and a drug retaining matrix, the backing protecting the adhesive and matrix and the adhesive holding the whole on the skin of the patient. On contact with the skin, the drug-retaining matrix delivers drug to the skin, the drug then passing through the skin into the patient's system.

The term "treat," "treating," or "treatment" as used herein means to counteract a medical condition (*e.g.*, a movement disorder) to the extent that the medical condition is

improved according to clinically acceptable standard(s). For example, "to treat a movement disorder" means to improve the movement disorder or relieve symptoms of the particular movement disorder in a patient, wherein the improvement and relief are evaluated with a clinically acceptable standardized test (*e.g.*, a patient self-assessment scale) and/or an empirical test (*e.g.*, PET scan). "Treatment" herein embraces prophylactic treatment unless the context requires otherwise.

The term "water-soluble" herein means having solubility of at least about 10 mg/ml. Unless otherwise specified, "solubility" herein means solubility in water at 20-25°C at any physiologically acceptable pH, for example at any pH in the range of about 4 to about 8. In the case of a salt, reference herein to solubility in water pertains to the salt, not to the free base form of pramipexole.

III. *Exemplary Uses of the Dosage Forms*

In various embodiments, the present invention contemplates modes of treatment and/or prophylaxis (*e.g.*, treating or preventing the development of symptoms in high-risk populations), which utilize one or more of the subject dosage forms for decreasing or overcoming the defects in a movement disorder patient. The improvement and/or restoration of mental or physical state in an organism has positive behavioral, social, and psychological consequences.

For example, Parkinson's disease is the second most common neurodegenerative disorder, affecting nearly 1 million people in North America. The disease is characterized by symptoms such as muscle rigidity, tremor and bradykinesia. Early studies of Parkinson's disease showed unusual inclusions in the cytoplasm of neurons (*i.e.*, Lewy bodies), occurring predominantly in the substantia nigra, which innervate the striatal region of the forebrain. Although Lewy bodies were also found in other neurodegenerative conditions, the presence of Lewy bodies in Parkinson's disease is accompanied by cell loss in the substantia nigra. This cell loss is considered to be the defining pathological feature of Parkinson's disease.

Epidemiological studies have reported geographic variation in Parkinson's disease incidence, leading to the search for environmental factors (Olanow and Tatton, *Ann. Rev. Neurosci.* **22**: 123-144, 1998). The recent discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxin causes a Parkinson's-like syndrome indistinguishable from the idiopathic disease suggests that Parkinson's disease may be caused by environmental factors (*e.g.*, toxins and causative agents). (See *e.g.*, Langston, *Ann. Neurol.* **44**: S45-S52,

1998).

Recent research has also identified genes associated with Parkinson's disease (Mizuno *et al.*, *Biomed. Pharmacother.* **53(3)**: 109-116, 1999; Dunnett and Bjorklund, *Nature* **399 (6738 Suppl)**: A32-A39, 1999); namely, the α-synuclein gene (Polymeropouos *et al.*, *Science* **276**: 2045-2047, 1997), the parkin gene (Kitada *et al.*, *Nature* **392**: 605-608, 1998), and the UCH-L1 thiol protease gene (Leroy *et al.*, *Nature* **395**: 451-452, 1998). Although additional chromosomal loci associated with the disease state have been identified, these chromosomal loci have not been analyzed at the molecular level. At present, the biochemical roles played by these gene products in both normal cells and in diseased neurons remain ambiguous, and no gene therapy protocols involving their use have been developed.

Furthermore, Parkinson's disease is associated with the progressive loss of dopamine neurons in the ventral mesencephalon of the substantia nigra (Shoulson, *Science* **282**: 1072-1074, 1998), which innervates the major motor-control center of the forebrain, the striatum. Although a gradual decline in the number of neurons and dopamine content of the basal ganglia is normally associated with increasing age, progressive dopamine loss is pronounced in people suffering from Parkinson's disease, resulting in the appearance of symptoms when about 70-80% of striatal dopamine and 50% of nigral dopamine neurons are lost (Dunnett and Bjorklund, *supra*). This loss of dopamine-producing neurons resulting in a dopamine deficiency is believed to be responsible for the motor symptoms of Parkinson's disease.

Although the cause of dopaminergic cell death remains unknown, it is believed that dopaminergic cell death is affected by a combination of necrotic and apoptotic cell death. Mechanisms and signals responsible for the progressive degeneration of nigral dopamine neurons in Parkinson's disease have been proposed (Olanow *et al.*, *Ann. Neurol.* **44**: S1-S196, 1998), and include oxidative stress (from the generation of reactive oxygen species), mitochondrial dysfunction, excitotoxicity, calcium imbalance, inflammatory changes and apoptosis as contributory and interdependent factors in Parkinson's disease neuronal cell death.

Apoptosis (*i.e.*, programmed cell death) plays a fundamental role in the development of the nervous system (Oppenheim, *Ann. Rev. Neurosci.* **14**: 453-501, 1991), and accelerated apoptosis is believed to underlie many neurodegenerative diseases, including Parkinson's disease (Barinaga, *Science* **281**: 1303-1304, 1998; Mochizuki *et al.*, *J. Neurol.*

Sci. **137**: 120-123, 1996; and Oo *et al.*, *Neuroscience* **69**: 893-901, 1995). In living systems, apoptotic death can be initiated by a variety of external stimuli, and the biochemical nature of the intracellular apoptosis effectors is at least partially understood.

In a further embodiment, a composition of the invention is administered in combination therapy with one or more additional drugs or prodrugs. The term "combination therapy" or "conjoint therapy" herein means a treatment regimen wherein the agent provided by the composition of the invention and a second agent are administered individually or together, sequentially or simultaneously, in such a way as to provide a beneficial effect from co-action of these therapeutic agents. Such beneficial effect can include, but is not limited to, pharmacokinetic or pharmacodynamic co-action of the therapeutic agents. Combination therapy can, for example, enable administration of a lower dose of one or both agents than would normally be administered during monotherapy, thus decreasing risk or incidence of adverse effects associated with higher doses. Alternatively, combination therapy can result in increased therapeutic effect at the normal dose of each agent in monotherapy.

Compositions of the invention can be especially suited to combination therapies, particularly where the second agent is one that is, or can be, administered once daily. There are significant advantages in patient convenience and compliance where both components of a combination therapy can be administered at the same time and with the same frequency. This is especially true in the case of geriatric patients or those suffering memory impairment.

When administered simultaneously, the two components of the combination therapy can be administered in separate dosage forms or in coformulation, *i.e.*, in a single dosage form, When administered sequentially or in separate dosage forms, the second agent can be administered by any suitable route and in any pharmaceutically acceptable dosage form, for example by a route and/or in a dosage form other than the present composition. In a preferred embodiment, both components of the combination therapy are formulated together in a single dosage form.

The second components of the subject combination therapy, *e.g.*, drugs useful for the treatment Parkinson's disease and other movement disorders, include L-dopa, selegiline, apomorphine and anticholinergics. L-dopa (levo-dihydroxy-phenylalanine) is a dopamine precursor which can cross the blood-brain barrier and be converted to dopamine in the brain. Unfortunately, L-dopa has a short half life in the body and it is typical after long use

(*i.e.*, after about 4-5 years) for the effect of L-dopa to become sporadic and unpredictable, resulting in fluctuations in motor function, dyskinesias and psychiatric side effects. Additionally, L-dopa can cause B vitamin deficiencies to arise.

The gastrointestinal absorption of orally administered levodopa depends on the gastrointestinal transit rates as absorption occurs primarily in the proximal third of the intestine (duodenum/jejunum) and not in the stomach (Rivera-Calimlim et al. Europ. J. Clin. Invest. 1, 1313-1320, 1971). Therefore a delayed release dosage form containing levodopa/carbidopa or levodopa/carbidopa/entacapone with pramipexole will allow the levodopa to be released in the target proximal intestine region and release levodopa is a sustained manner similar to enteral infusion of levodopa.

Thus in certain embodiments, the invention provides a pharmaceutical composition comprising pramipexole and levodopa (optionally also carbidopa or a prodrug thereof) for treating PD and other related movement disorders. The invention also provides methods of using such pharmaceutical compositions for treating PD and other related movement disorders. See Examples 86-89.

Selegiline (Deprenyl, Eldepryl) has been used as an alternative to L-dopa, and acts by reducing the breakdown of dopamine in the brain. Unfortunately, selegiline becomes ineffective after about nine months of use. Apomorphine, a dopamine receptor agonist, has been used to treat Parkinson's disease, although is causes severe vomiting when used on its own, as well as skin reactions, infection, drowsiness and some psychiatric side effects.

Systemically administered anticholinergic drugs (such as benzhexol and orphenedrine) have also been used to treat Parkinson's disease and act by reducing the amount of acetylcholine produced in the brain and thereby redress the dopamine/acetylcholine imbalance present in Parkinson's disease. Unfortunately, about 70% of patients taking systemically administered anticholinergics develop serious neuropsychiatric side effects, including hallucinations, as well as dyskinetic movements, and other effects resulting from wide anticholinergic distribution, including vision effects, difficulty swallowing, dry mouth, and urine retention. See *e.g.* Playfer, *Parkinson's Disease, Postgrad Med J* **73**: 257-264, 1997 and Nadeau, *Parkinson's Disease, J Am Ger Soc* **45**: 233-240, 1997.

Newer drug refinements and developments include direct-acting dopamine agonists, slow-release L-dopa formulations, inhibitors of the dopamine degrading enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAO-B), and dopamine

transport blockers. These treatments enhance central dopaminergic neurotransmission during the early stages of Parkinson's disease, ameliorate symptoms associated with Parkinson's disease, and temporarily improve the quality of life. However, despite improvements in the use of L-dopa for treating Parkinson's disease, the benefits accorded by these dopaminergic therapies are temporary, and their efficacy declines with disease progression. In addition, these treatments are accompanied by severe adverse motor and mental effects, most notably dyskinesias at peak dose and "on-off" fluctuations in drug effectiveness (Poewe and Granata, in *Movement Disorders. Neurological Principles and Practice* (Watts and Koller, eds) McGraw-Hill, New York, 1997; and Marsden and Parkes, *Lancet* **1**: 345-349, 1977). No drug treatments are currently available that lessen the progressive pace of nigrostriatal degeneration, postpone the onset of illness, or that substantively slow disability (Shoulson, *supra*).

Other methods for the treatment of Parkinson's disease involve neurosurgical intervention, such as thalamotomy, pallidotomy, and deep brain stimulation. The thalamic outputs of the basal ganglia are an effective lesion target for the control of tremor (*i.e.*, thalamotomy). Thalamotomy destroys part of the thalamus, a brain region involved in movement control. Unilateral stereotactic thalamotomy has proven to be effective for controlling contralateral tremor and rigidity, but carries a risk of hemiparesis. Bilateral thalamotomy carries an increased risk of speech and swallowing disorders resulting.

Stereotactic pallidotomy, surgical ablation of part of the globus pallidus (a basal ganglia), has also be used with some success. Pallidotomy is performed by inserting a wire probe into the globus pallidus and heating the probe to destroy nearby tissue. Pallidotomy is most useful for the treatment of peak-dose diskinesias and for dystonia that occurs at the end of a dose.

Aside from surgical resection, deep brain stimulation, high frequency stimulating electrodes placed in the ventral intermedialis nucleus, has been found to suppress abnormal movements in some cases. A variety of techniques exist to permit precise location of a probe, including computed tomography and magnetic resonance imaging. Unfortunately, the akinesia, speech and gait disorder symptoms of Parkinson's disease are little helped by these surgical procedures, all of which result in destructive brain lesions. Despite the development of modem imaging and surgical techniques to improve the effectiveness of these neurosurgical interventions for the treatment of Parkinson's disease tremor symptoms, the use of neurosurgical therapies is not widely applicable. For example, thalamotomy does

not alleviate the akinetic symptoms which are the major functional disability for many people suffering from Parkinson's disease (Marsden *et al.*, *Adv. Neurol.* **74**: 143-147, 1997).

Therapeutic methods aimed at controlling suspected causative factors associated with Parkinson's disease (*e.g.*, therapies which control oxidative stress and excitotoxicity) have also been developed. Clinical trials have shown that administration of antioxidative agents vitamin E and deprenyl provided little or no neuroprotective function (Shoulson *et al.*, *Ann. Neurol.* **43**: 318-325, 1998). Glutamate-receptor blockers and neuronal nitric oxide synthase (NOS) inhibitors have been proposed as therapies for Parkinson's disease; however, no experimental results from human studies have yet been published (Rodriguez, *Ann. Neurol.* **44**: S175-S188, 1998).

The use of neurotrophic factors to stimulate neuronal repair, survival, and growth in Parkinson's disease has also been studied, particularly the use of glial cell line-derived neurotrophic factor (GDNF). Although GDNF protein protects some dopamine neurons from death, it is difficult to supply GDNF protein to the brain. Furthermore, the use of such protein therapies in general is problematic, since protein molecules show rapid *in vivo* degradation, are unable to penetrate the blood-brain barrier, and must be directly injected into the ventricles of the patient's brain (Palfi *et al.*, *Soc. Neurosci. Abstr.* **24**: 41, 1998; Hagg, *Exp. Neurol.* **149**: 183-192, 1998; and Dunnett and Bjorklund, *supra*). Other neurotrophic factors which may have therapeutic value have been proposed based on *in vitro* and animal model systems, including neurturin, basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF), neurotrophins 3 and 4/5, ciliary neurotrophic factor and transforming growth factor ß (TGF-ß). However, the effectiveness of these therapies in humans remains unknown. At present, no single chemical compound or peptide has been reported to completely protect dopamine neurons from death by tropic factor withdrawal or neurotoxin exposure.

Cell replacement therapies have also received much attention as potential methods for treating Parkinson's disease (Freed *et al.*, *Arch. Neurol.* **47**: 505-512, 1990; Freed *et al.*, *N. Engl. J. Med.* **327**: 1549-1555, 1992; Lindvall *et al.*, *Science* **247**: 574-577, 1990; Spencer *et al.*, *N. Engl. J. Med.* **327**: 1541-1548, 1992; Widner *et al.*, *N. Engl. J. Med.* **327**: 1556-1563, 1992; Lindvall, *NeuroReport* **8**: iii-x, 1997; Olanow *et al.*, *Adv. Neurol.* **74**: 249-269, 1997; and Lindvall, *Nature Biotechn.* **17**: 635-636, 1999). These neural grafting therapies use dopamine supplied from cells implanted into the striatum as a substitute for nigrostriatal dopaminergic neurons that have been lost due to neurodegeneration. Although

animal models and preliminary human clinical studies have shown that cell replacement therapies may be useful in the treatment of Parkinson's disease, the failure of the transplanted neurons to survive in the striatum is a major impediment in the development of cell replacement therapies.

Various sources of dopaminergic neurons for use in the transplantation process have been tried in animal experiments, including the use of mesencephalic dopamine neurons obtained from human embryo cadavers, immature neuronal precursor cells (*i.e.*, neuronal stem cells), dopamine secreting non-neuronal cells, terminally differentiated teratocarcinoma-derived neuronal cell lines (Dunnett and Bjorkland, *supra*), genetically modified cells (Raymon *et al.*, *Exp. Neurol.* **144**: 82-91, 1997; and Kang, *Mov. Dis.* **13**: 59-72, 1998), cells from cloned embryos (Zawada *et al.*, *Nature Medicine* **4**: 569-573, 1998) and xenogenic cells (Bjorklund *et al.*, *Nature* **298**: 652-654, 1982; Huffaker *et al.*, *Exp. Brain Res.* **77**: 329-336, 1989; Galpem *et al.*, *Exp. Neurol.* **140**: 1-13, 1996; Deacon *et al.*, *Nature Med.* **3**: 350-353, 1997; and Zawada *et al.*, *Nature Med.* **4**: 569-573, 1998). Nonetheless, in current grafting protocols, no more than 5-20% of the transplanted dopamine neurons survive.

Additional therapies are also available, such as physical therapy, occupational therapy, or speech / language therapy. Exercise, diet, nutrition, patient/caregiver education, and psychosocial interventions have also been shown to have a positive effect on the mental and/or physical state of a person suffering from Parkinson's disease.

Various methods of evaluating Parkinson's disease in a patient include Hoehn and Yahr Staging of Parkinson's Disease, Unified Parkinson Disease Rating Scale (UPDRS), and Schwab and England Activities of Daily Living Scale.

A person suffering from Parkinson's disease should avoid contraindicated and potentially contraindicated drugs such as antipsychotic drugs, Haloperidol (Haldol), Perphenazine (Trilafon), Chlorpromazine (Thorazine), Trifluoperazine (Stelazine), Flufenazine (Prolixin, Permitil) Thiothixene (Navane), Thioridazine (Mellaril); antidepressant drug, combination of Perphenazine and Amitriptyline (Triavil); anti-vomiting drugs, Prochlorperazine (Compazine), Metoclopramide (Reglan, Maxeran), Thiethylperazine (Torecan), Reserpine (Serpasil), Tetrabenazine (Nitoman); blood pressure drug, Alpha-methyldopa (Aldomet); anti-seizure drug, Phenytoin (Dilantin); mood stabilizing drug, lithium; and anti-anxiety drug, Buspirone (Buspar).

IV. *Exemplary Levodopa/Carbidopa Pharmaceutical Compositions for First Immediate-*

Release Portion, Second Substantial Zero-order Release Portion, and Second IR or Substantially Ascending Release Portion

Certain embodiments of the invention provides a pharmaceutical preparation comprising an oral dosage formulation in a therapeutically effective amount sufficient to treat movement disorder (*e.g.,* Parkinson's disease or another movement disorder) in a patient, wherein the dosage formulation, when administered to the patient, provides a treatment regimen characterized by a rapid (immediate) release portion that quickly (*e.g.*, in less than about 2 hours, *e.g.*, in less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*, after administration) boosts effective levodopa concentration to a therapeutically effective level, followed by a substantially sustained dose (zero-order release dose) over at least about 2 hours, 4 hours, 6 hours, 8, hours, 12 hours, 16 hours, 20 hours, or at least about 24 hours. Optionally, a substantially ascending portion, such as a second IR portion, is also provided subsequent to the second zero-order release portion to ensure a rapid drop at the end of the therapeutic regimen cycle (*e.g.*, at day end, or before the patient goes to bed).

Certain embodiments of the invention provide a pharmaceutical preparation / dosage formulation provided in the form of a transdermal patch and formulated for sustained release formulation, in a therapeutically effective amount sufficient to treat a movement disorder (*e.g.,* Parkinson's disease and related movement disorders) in a patient, wherein the dosage formulation, when administered (provided as a patch) to the patient, provides a substantially sustained dose over at least about 2 hours, 4 hours, 6 hours, 8, hours, 12 hours, 20 hours, or at least about 24 hours.

For the treatment of Parkinson's disease, the first IR portion preferably contains a relatively high ratio of decarboxylase inhibitor (*e.g.*, carbidopa) / levodopa. In case of carbidopa / levodopa, the ratio is preferably > 1:4, or 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 or higher. The first IR is formulated to quickly release the compositions such that an effective therapeutic concentration of levodopa is reached in less than about 2 hours (*e.g.*, in less than about 1 minute, 5 min., 10 min., 15 min., 20 min., 30 min., 45 min., 1 hour, 1.5 hours, 2 hours, *etc.*, or within a range of time bounded by any of these time periods, *e.g.*, 1 min. to 2 hours, 5 min. to 1 hour, 15 to 20 min., *etc.*) of administration.

In certain embodiments, carbidopa may be administered before release of the first IR portion of levodopa, thereby more effectively inhibiting peripheral decarboxylase activity

and maximizing the efficacy of the levodopa in the first IR portion. For example, there may be a layer comprising carbidopa that is released prior to the first IR portion, carbidopa in the IR portion may be formulated to release faster than the levodopa in the IR portion (*e.g.*, higher release ratio of carbidopa/levodopa), or a bioadhesive layer comprising a high proportion of carbidopa that at least partially undergoes immediate release may be present. Alternatively, the carbidopa may be administered as a separate formulation, *e.g.*, together with a levodopa composition coated with a delayed release coating.

The second sustained release (zero-order release) portion may contain a single uniform composition (*e.g.*, with a uniform ratio of carbidopa / levodopa throughout). Alternatively, the second substantially zero order release portion may have a gradient of carbidopa / levodopa ratio from start to finish. For example, the ratio may approach 1:4 at the beginning of the second portion, but drop continuously or discontinuously to, for example, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, or 1:20, *etc.* If there is a discontinuous drop, the second portion may comprise several sub-portions, each possibly having a unique carbidopa / levodopa ratio.

The rapidly ascending release portion (such as the second IR portion) may contain no carbidopa, or fairly low ratio of carbidopa / levodopa, such that a rapid drop in effective levodopa concentration may be achieved, thus avoiding the long-tail effect that interferes with patient sleeping or rest.

In addition to carbidopa / levodopa, the portions of the subject dosage forms may additionally comprise compositions other than pharmaceutically acceptable carriers, exipients, or diluents, *etc.* (see details below). Such additional compositions may comprise a dopamine transporter inhibitor to be released with a delay. Such additional compositions may also comprise other pharmaceutical compositions useful for treating Parkinson's disease (*e.g.*, in conjoint therapy).

In either oral or patch form, the above-described dosage preparation can be one wherein the pharmaceutical composition is formulated in a multiplicity of (sub-)portions or polymeric layers. For example, in certain embodiments, the second sustained release portion may comprise a multiplicity of layers such that the preparation optionally delivers to the patient a sustained release portion with varying ratios of decarboxylase / levodopa over time, even when the amount of released levodopa remains largely constant. Thus, the subject pharmaceutical composition can be provided in an initial portion (*e.g.*, for immediate-release or IR), followed by a second portion (*e.g.*, substantially zero-order

sustained release or SR, optionally with more than one sub-portions or a continuously changing ratio of inhibitor / levodopa), and a final portion (*e.g.*, an additional immediate-release portion), whereby the preparation delivers the initial dose, the second dose, then a final dose over time.

In other embodiments, the dose preparation can also be a plurality of beads, each bead including a subject pharmaceutical composition independently having a dissolution profile, which plurality of beads is a variegated population with respect to ratios of the pharmaceutical composition and/or dissolution profile, so as deliver, upon administration, the immediate, sustained, and increasing dose of the subject pharmaceutical composition. Several exemplary embodiments of the dosage forms are described in more details below.

In still other embodiments, the dose preparation is generated such that the subject pharmaceutical composition is (i) contained within a nonabsorbable shell that releases the drug at a controlled rate, and (ii) formulated in at least two different dissolution profiles.

In certain embodiments, the dosage formulations of the present invention have a side-effect therapeutic index, (SeD_{50}/ED_{50}), such as with respect to the movement disorder, that is at least 2 times greater than the same amount of drug provided in immediate release form, and more preferably at least 5, 10 or even 100 times greater.

In certain embodiments, the subject packages, preparations, pharmaceutical compositions, and methods for the treatment of movement disorders further comprise one or more therapeutic agents for treating Parkinson's disease selected from a dopamine precursor, such as L-dopa; a dopaminergic agent, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a dopaminergic and anti-cholinergic agent, such as amantadine (SYMMETRYL®, SYMADINE®); an anti-cholinergic agent, such as trihexyphenidyl (ARTANE®), benztropine (COGENTIN®), ethopropazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopamine agonist, such as apomorphine, bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), lisuride (DOPERGINE®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a MAO-B (monoamine oxidase B) inhibitor, such as selegiline or deprenyl (ATAPRYL®, CARBEX®, ELDEPRYL®); a COMT (catechol O-methyltransferase) inhibitor, such as CGP-28014, tolcapone (TASMAR®) or entacapone (COMTAN®); or other therapeutic agents, such as baclofen (LIORESAL®), domperidone (MOTILIUM®), fludrocortisone (FLORINEF®), midodrine (AMATINE®), oxybutynin (DITROPAN®), propranolol (INDERAL®, INDERAL-LA®),

clonazepam (RIVOTRIL®), or yohimbine.

The subject treatment may also be used either in conjoint therapy with, or additionally include one or more other pharmaceutical compositions, such as the ones described below.

For example, US20030045539 (incorporated herein by reference) discloses a combination treatment of cabergoline and pramipexole provided concurrently to a patient suffering from various central nervous system diseases, and in particular for the treatment of Parkinson's Disease (PD). The initial dose of cabergoline is administered to the patient at a dose of 0.5 to 1 mg/patient/day and is adjusted upward at weekly intervals to a therapeutic dosage of 2, 4, 6, 8 or 10 mg/patient/day and where the initial dose of pramipexole is started at 0.375 mg/patient/day and is adjusted upward every 5 to 7 days to a therapeutic dosage of 3, 4, 5, 6, or 7 mg/patient/day. At least one portion of the subject pharmaceutical composition may additional comprise cabergoline and pramipexole for treating Parkinson's disease.

US20040166159 (incorporated herein by reference) discloses a pharmaceutical dosage forms having immediate and controlled release properties that contain an aromatic amino acid decarboxylase (AAAD) inhibitor (such as carbidopa), levodopa, and optionally a catechol-O-methyltransferase (COMT) inhibitor, for the treatment of medical conditions associated with reduced dopamine levels in a patient's brain. The dosage form may comprise up to about 1000 mg, or about 20-500 mg, about 50-500 mg, or about 100-200 mg of COMT inhibitor. The COMT inhibitor may be contained only within the immediate release component, or only within the sustained release component, or both. The COMT inhibitor may be CGP-28014, entacapone, or tolcapone. The dosage form may further comprise one or more drugs such as anti-cholinergics, beta 2-agonists, cyclooxygenase-2 (COX-2) inhibitors, dopamine receptor agonists, monoamine oxidase (MAO) inhibitors, opiate delta receptor agonists, opiate delta receptor antagonists, and N-methyl-D-aspartate (NMDA) antagonists. The dosage form may further comprise one or more drugs selected from albuterol, alpha-lipoic acid, amantadine, andropinirole, apomorphine, baclofen, biperiden, benztropine, bromocriptine, budipine, cabergoline, clozapine, deprenyl, dextromethorphan, dihydroergokryptine, dihydrolipoic acid, eliprodil, eptastigmine, ergoline, formoterol, galanthamine, lazabemide, lysuride, mazindol, memantine, mofegiline, orphenadrine, pergolide, pirbuterol, pramipexole, propentofylline, procyclidine, rasagiline, remacemide, riluzole, rimantadine, ropinirole, salmeterol, selegiline, spheramine, terguride,

and trihexyphenidyl.

Similarly, other movement disorders may also be treated with similar methods and suitable pharmaceutical compositions, such as the ones described below.

For example, in certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating dystonia selected from an anti-cholinergic agent, such as trihexyphenidyl (ARTANE®), benztropine (COGENTIN®), ethopropazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopaminergic agent, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a muscle relaxant, such as baclofen (LIORESAL®); a sedative, such as Clonazepam (RIVOTRIL®); an anticonvulsant agent, such as carbamazepine (TEGRETOL®); a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®); or a dopamine blocker, such as haloperidol (HALDOL®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating tremor selected from a β-blocker, such as propranolol (INDERAL®, INDERAL-LA®); an anticonvulsant agent, such as primidone (MYSOLINE®); or a carbonic anhydrase inhibitor, such as acetalzolamide (DIAMOX®) or methazolamide (NEPTAZANE®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating myoclonus selected from a sedative, such as clonazepam (RIVOTRIL®); or an anticonvulsant agent, such as valproic acid (EPIVAL®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating chorea selected from a dopamine blocker, such as haloperidol (HALDOL®); or a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®).

In certain embodiments of the packages, preparations, compositions, and methods for the treatment of a movement disorder, the invention further comprises one or more therapeutic agents for treating restless leg syndrome selected from a dopaminergic, such as Levodopa-carbidopa (SINEMET®, SINEMET CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a sedative, such as clonazepam (RIVOTRIL®); a dopamine agonists, such as bromocriptine (PARLODEL®), pergolide

(PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a narcotic agent, such as codeine (TYLENOL # 3®); or a GABAergic agent, such as gabapentin (NEURONTIN®).

In certain embodiments of the subject packages, preparations, compositions, and methods for the treatment of movement disorders, the invention further comprises one or more therapeutic agents for treating tics selected from a sedative, such as clonazepam (RIVOTRIL®); an alpha antagonist, such as clonidine (CATAPRESS®); a dopamine reuptake inhibitor, such as tetrabenazine (NITOMAN®); or a dopamine blocker, such as haloperidol (HALDOL®) or perphenazine.

In certain embodiments, the present invention provides pharmaceutical preparations comprising, as an active ingredient, an enantiomerically enriched preparation of R-(-) amphetamine or a derivative thereof. The subject amphetamine compound is formulated in an amount sufficient to treat or prevent a movement disorder in an animal.

Still another embodiment of the invention relates to the use of enantiomerically enriched preparations of amphetamine compounds for lessening the severity or prophylactically preventing the occurrence of movement disorders in an animal, and thus, altering the mental or physical state of the animal. The compounds of the present invention may also be useful for treating and/or preventing memory impairment, *e.g.*, due to a movement disorder.

It should be noted that levodopa and carbidopa of the subject pharmaceutical composition can be replaced in whole or in part in this invention with appropriate prodrugs, stereoisomers, acceptable salts, hydrates, solvates, *etc.* Levodopa prodrugs include any pharmaceutically suitable ester of levodopa such as, but not limited to, the methyl, ethyl, or propyl esters of levodopa, or combinations thereof. Levodopa may be in the form of (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid, 3-hydroxy-L-tyrosine ethyl ester, phenylglycine, or a mixture thereof. The following specific examples describe levodopa prodrugs and carbidopa prodrugs, as well as additional compositions (such as fillers, organic acids, metals, metal chelators, *etc.*) that might constitute useful supplements to the backbone levodopa / carbidopa composition. These compositions may be used as the subject pharmaceutical composition.

For example, US20020151589A1 (incorporated herein by reference) describes a dispersible pharmaceutical composition comprising a therapeutically effective amount of L-DOPA ethyl ester, a therapeutically effective amount of a decarboxylase inhibitor, a filler, a disintegrant, and a lubricant, and a method of preparing the pharmaceutical composition

described herein. The filler may be corn starch, glucose, various natural gums, methylcellulose, carboxymethylcellulose, microcrystalline cellulose, calcium phosphate, calcium carbonate, calcium sulfate kaolin, sodium chloride, powdered cellulose, sucrose, mannitol and starch, preferably microcrystalline cellulose (with a moisture content of up to about 1.5%, or up to about 5.0%). The decarboxylase inhibitor may be carbidopa (with a moisture content of, for example, between 5.0-10.0%, preferably 7.5%) or benserazide. The disintegrant may be kaolin, starch, powdered sugar, sodium starch glycolate, crosscarmelose sodium, carboxymethyl cellulose, microcrystalline cellulose and sodium alginate, preferably pregelatinized starch (with a moisture content of up to about 5, 7, 12, or 14%). The lubricant may be talc, sodium stearyl fumarate, magnesium stearate, calcium stearate, hydrogenated castor oil, hydrogenated soybean oil, and polyethylene glycol, preferably magnesium stearate. The excipient may be a binding agent such as sorbitol, glucose, xylitol, and mannitol. The composition may further comprise an antioxidant such as tocopherol, sodium metabisulphite, butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid and sodium ascorbate, preferably sodium metabisulphite. Various weight percentages and amounts per dose are also disclosed, and incorporated herein by reference. Such levodopa ethyl ester and the other described components may be used as the levodopa composition of the invention.

In another example, US20020192290A1 (incorporated herein by reference) discloses a pharmaceutical composition comprising a therapeutically effective amount of levodopa and of carbidopa, dispersed in a hydrophilic matrix, the composition further comprising an organic acid. The process for preparing the composition, comprising granulation, in particular in a fluidized bed, of the various components and compression of the granules obtained, is also disclosed. The organic acid may be fumaric acid, citric acid, ascorbic acid, maleic acid, glutamic acid, malonic acid and oxalic acid. The organic acid may represent from 0.2% to 20% by weight relative to the weight of the composition. The hydrophilic matrix (such as hydroxypropylmethyl cellulose) may represent from 10% to 80% by weight relative to the weight of the composition. The hydrophilic matrix may also comprise an insoluble substance, such as microcrystalline cellulose.

US20040028613A1 (incorporated herein by reference) discloses formulation useful for enhancing peak concentrations in CNS tissues or fluids and for treating, for example, Parkinson's disease, comprises dopamine agonist and at least one delivery enhancing agent. The dopamine receptor agonist may be apomorphine or a pharmaceutically acceptable salt

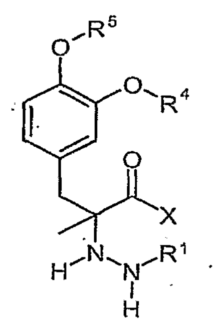
or derivative thereof, and is administered to the subject in an effective dose of between about 0.25 and 2.0 mg. The delivery-enhancing agent(s) is/are selected from: (a) an aggregation inhibitory agent; (b) a charge modifying agent; (c) a pH control agent; (d) a degradative enzyme inhibitory agent; (e) a mucolytic or mucus clearing agent; (f) a ciliostatic agent; (g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (ii) a phospholipid additive, mixed micelle, liposome, or carrier, (iii) an alcohol, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a clyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x); (h) a modulatory agent of epithelial junction physiology; (i) a vasodilator agent; (j) a selective transport-enhancing agent; and (k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the dopamine receptor agonist is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the dopamine receptor agonist for enhanced mucosal delivery, wherein the formulation of the dopamine receptor agonist with the one or more delivery-enhancing agents provides for increased bioavailability of the dopamine receptor agonist in a central nervous system tissue or fluid of the subject. The delivery-enhancing agent(s) may also be selected from citric acid, sodium citrate, propylene glycol, glycerin, L-ascorbic acid, sodium metabisulfite, edetate disodium, benzalkonium chloride, sodium hydroxide and mixtures thereof.

US20050070608 (incorporated herein by reference) discloses a composition useful for treating dopamine disorders, *e.g.*, Parkinson's disease, comprises levodopa, carbidopa, acid and optionally metal chelator or thioether compound. The metal chelator may be EDTA, or deferoxamine mesylate. The EDTA may be in the form of a salt of a free base, and/or at a concentration of at least about 0.01 mg/ml. The acid may be a carboxylic acid, a mineral acid, citric acid, tartaric acid, ascorbic acid, dehydroascorbic acid, acetic acid (ethanoic acid), formic acid (methanoic acid), butyric acid (butanoic acid), benzoic acid, malic acid, propionic acid, epoxysuccinic acid, muconic acid, furanacrylic acid, citramalic acid, capric acid, stearic acid, caproic acid, malonic acid, succinic acid, diethylacetic acid,

methylbutryic acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, and sulfuric acid, but preferably not ascorbic acid. The composition does not contain sugar. The composition may be a liquid. Preferably, less than 10%, or 5% of the carbidopa has degraded at 25°C after 7 days, or less than 10% of the carbidopa has degraded at 25°C after 30 days, or less than 5% of the carbidopa has degraded at 25°C after 4 days. The composition may further comprise an artificial sweetener, such as aspartame. The composition may further comprise a preservative, such as sodium benzoate. The composition may be clear or translucent.

US20040167216 and its PCT counterpart WO04/052841A1 (both incorporated herein by reference) discloses prodrugs of carbidopa, derivatives of carbidopa prodrugs, methods of making and using such prodrugs and derivatives thereof, and compositions of such prodrugs and derivatives thereof. All such prodrugs may be used as carbidopa substitutes in the instant invention.

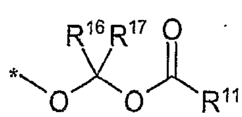
For example, in one embodiment, the prodrug is compound of Formula (I):



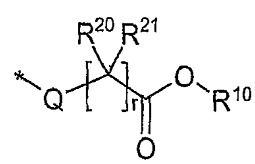
(I)

a stereoisomer thereof, an enantiomer thereof, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate of any of the foregoing, wherein:

X is selected from $-OR^{10}$ and moieties of Formulae (II) and (III):

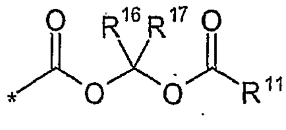


(II)



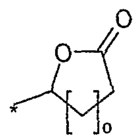
(III)

where: r is an integer from 1 to 6; Q is O or $-NR^{15}$; $-R^1$ is selected from hydrogen and a moiety comprising Formula (IX):

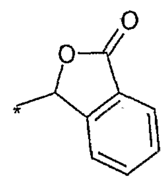


(IX)

R^4 and R^5 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, - $C(O)OR^{27}$, -$C(O)R^{27}$, -$(CR^{16}R^{17})OC(O)R^{11}$ and moieties of Formulae (XVII) and (XVIII):

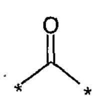


(XVII)

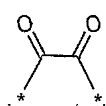


(XVIII)

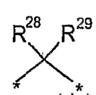
wherein o is 1-3, and the cycloheteroalkyl rings in (XVII) and (XVTII) are optionally substituted with one or more groups selected from halo, CN, NO_2, OH, C_{1-6} alkyl, and C_{1-6} alkoxy; or R^4 and R^5 together form a structure selected from Formulae (XII) to (XVI):



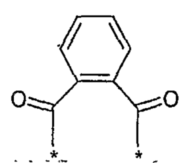
(XII)



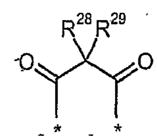
(XIII)



(XIV)



(XV)



(XVI)

wherein the aryl ring in Formula (XV) is optionally substituted with one or more groups selected from halo, CN, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and -CO_2R^{31};

R^{10} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{11} is selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or

optionally, R^{11} and either R^{16} or R^{17}, together with the atoms to which R^{11}, and either R^{16} or R^{17} are attached, form a cycloheteroalkyl or substituted cycloheteroalkyl ring, optionally to which is fused an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{15} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, and substituted arylalkyl;

R^{16} and R^{17} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbomoyl, cycloalkyl, substituted cycloalkyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl or optionally, R^{16} and R^{17} together with the carbon atom to which R^{16} and R^{17} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring; each R^{20} and R^{21} is independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, alkylamino, substituted alkylarnino, alklysulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy, and substituted heteroaryloxy, or optionally, when r is 1, then R^{20} and R^{21} together with the carbon atom to which R^{20} and R^{21} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring, or optionally when R^{20} and R^{15} are present and are attached to adjacent atoms then R^{15} and R^{20} together with the atoms to which R^{15} and R^{20} are attached form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{27} is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{28} and R^{29} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroalkyl, and substituted heteroalkyl;

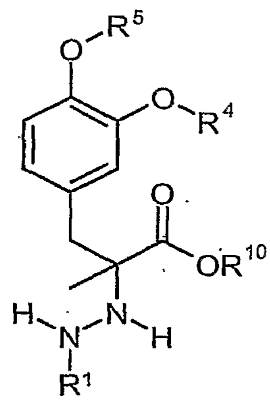
and R^{31} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

with the provisos that

when X is $-OR^{10}$, R^1 is hydrogen, and R^4 and R^5 are independently selected from hydrogen and C_{1-19} alkyl, C_{1-19} aryl or C_{1-19} arylalkyl, then R^{10} is not hydrogen or C_{1-6} alkyl; and

none of R^1, R^4, R^5, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{27}, R^{28}, R^{29}, and R^{31} comprise a bile acid moiety.

In another embodiment, the prodrug is a compound of Formula (Ia):



(Ia)

a stereoisomer thereof, an enantiomer thereof, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate of any of the foregoing, wherein:

R^1 is selected from hydrogen and the structure of Formula (IX): see above;

R^4 and R^5 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, $-C(O)OR^{27}$, $-C(O)R^{27}$, $-(CR^{16}R^{17})OC(O)R$ and moieties of Formulae (XVII) and (XVIII): see above;

wherein o is 1-3, and the cycloheteroalkyl rings in (XVII) and (XVIII) are optionally substituted with one or more groups selected from halo, CN, NO_2, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

or R^4 and R^5 together form a structure selected from Formulae (XII) to (XVI) (see above);

wherein the aryl ring in Formula (XV) is optionally substituted with one or more groups selected from halo, CN, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and $-CO_2R^{31}$;

R^{10} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{11} is selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^{11} and either R^{16} or R^{17}, together with the atoms to which R^{11}, and either R^{16} or R^{17} are attached, form a first cycloheteroalkyl or substituted cycloheteroalkyl ring, to which an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring is optionally fused to said first cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{16} or R^{17} are independently selected from hydrogen, alkyl, substituted alkyd, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroarylalkyl, and substituted heteroarylalkyl or optionally, R^{16} or R^{17} together with the carbon atoms to which R^{16} or R^{17} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{27} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{28} and R^{29} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroalkyl, and substituted heteroalkyl; and

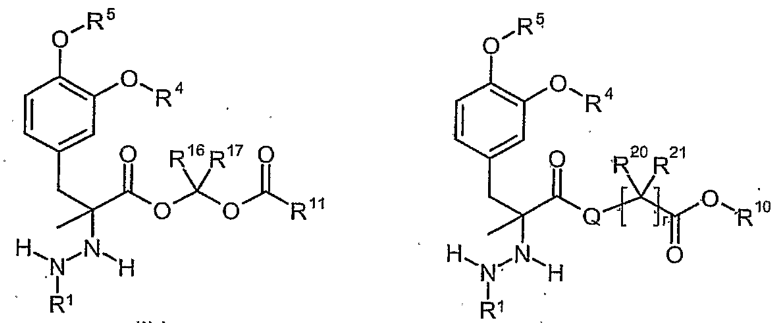
R^{31} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

with the provisos that

when R^1 hydrogen, and R^4 and R^5 are independently selected front hydrogen, - C_{1-19} alkyl, C1-19 aryl, or C_{1-19} arylalkyl, then R^{10} is not hydrogen or C_{1-6} alkyl; and

none of R^1, R^4, R^5, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{27}, R^{28}, R^{29}, and R^{31} comprise a bile acid moiety.

In yet another embodiment, the prodrug is a compound of Formulae (Ib) or (Ic):



(Ib) (Ic)

a stereoisomer thereof, an enantiomer thereof, a pharmaceutically acceptable salt thereof, a hydrate thereof, or a solvate of any of the foregoing, wherein:

Q is O or $-NR^{15}$;

r is an integer from 1 to 6;

R is selected from hydrogen and a moiety comprising Formula (IX) (see above);

R^4 and R^5 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroalkyl, substituted heteroalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, - $C(O)OR^{27}$, - $C(O)R^{27}$, $-(CR^{16}R^{17})OC(O)R^{11}$, and moieties of Formulae (XVII) and (XVIII) (see above);

wherein o is 1-3, and the cycloheteroalkyl rings in (XVII) and (XVIII) are optionally substituted with one or more groups selected from halo, CN, NO_2, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

or R^4 and R^5 together form a structure selected from Formulae (XII) to (XVI) (see above);

wherein the aryl ring in Formula (XV) is optionally substituted with one or more groups selected from halo, CN, OH, C_{1-6} alkyl, C_{1-6} alkoxy, and $-CO_2R^{31}$;

R^{10} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted

heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{11} is selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or optionally, R^{11} and either R^{16} or R^{17}, together with the atoms to which R^{11}, R^{16} and R^{17} are attached, form a cycloheteroalkyl or substituted cycloheteroalkyl ring, to which an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring is optionally fused to said cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{15} is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, and substituted arylalkyl;

R^{16} and R^{17} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroarylalkyl, and substituted heteroarylalkyl or optionally, R^{16} and R^{17} together with the carbon atoms to which R^{16} and R^{17} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

each R^{20} and R^{21} is independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, alkylamino, substituted alkylamino, alklysulfinyl, substituted alkylsulfnyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy, and substituted heteroaryloxy, or optionally, when r is 1, then R^{20} and R^{21} together with the carbon atom to which R^{20} and R^{21} are attached form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring, or optionally when R^{20} and R^{15} are present and are attached to adjacent atoms then R^{20} and R^{15} together with the atoms to which R^{20} and R^{15} are attached form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{27} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted

cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

R^{28} and R^{29} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroalkyl, and substituted heteroalkyl;

and R^{31} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl;

with the proviso that none of R^1, R^4, R^5, R^{10}, R^{11}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{27}, R^{28}, R^{29}, and R^{31} comprise a bile acid moiety.

V. *Other Exemplary Levodopa/Carbidopa Dosage Forms*

Many dosage forms in the art may be readily adapted for use in the instant invention according to the general teaching of the invention. The following describe certain levodopa ethyl esters or derivatives thereof, which may be used in the instant invention.

US20030152628 (incorporated herein by reference) discloses a tablet which comprises an inner core formulated for controlled release consisting essentially of a mixture of levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof, a carrier and an inner core excipient component; and an outer layer encapsulating the inner core and formulated for immediate release comprising a mixture of a decarboxylase inhibitor and levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof.

US20030147957 (incorporated herein by reference) discloses a tablet which comprises: an inner core formulated for controlled release comprising a mixture of (a) a granulated admixture of a decarboxylase inhibitor and a surfactant, and (b) levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof; and an outer layer encapsulating the inner core and formulated for immediate release comprising a mixture of a granulated decarboxylase inhibitor and levodopa ethyl ester or a derivative or a pharmaceutically acceptable salt thereof. It also provides methods of manufacturing such tablets.

US20040234608 (incorporated herein by reference) discloses a pharmaceutical composition for use in a dosage form for oral administration to a patient. The composition

expands upon contact with gastric fluid and promotes retention of the dosage form in the patient's stomach for a prolonged period of time. The application further provides pharmaceutical dosage forms containing an active ingredient, and the pharmaceutical composition. The forms are adapted for immediate or controlled release of the active ingredient. The dosage forms may be used advantageously in the treatment of Parkinson's disease with levodopa and hyperactivity and attention deficit disorder with methylphenidate. The composition comprises a hydrogel, a superdisintegrant and tannic acid wherein the volume of the composition increases about three fold within about 15 minutes of contacting gastric fluid. Its volume increases about 5-8 fold within about fifteen minutes of contacting gastric fluid, or increases about 3 fold within about five minutes of contacting gastric fluid. The hydrogel may comprise hydroxypropyl methylcellulose, and may further comprise hydroxypropyl cellulose, preferably in a weight ratio of from about 1:3 to about 5:3. The hydrogel may further comprise a cross-linked polyacrylate, such as a polyacrylic acid polymer crosslinked with allyl sucrose. The superdisintegrant may be selected from cross-linked carboxymethylcellulose sodium, sodium starch glycolate and cross-linked polyvinylpyrrolidone, preferably cross-linked carboxymethylcellulose sodium or sodium starch glycolate. The tannic acid may be present in an amount of from about 2 weight percent to about 12 weight percent of the total weight of hydrogel, superdisintegrant and tannic acid, exclusive of other excipients that may be present.

US20040180086 (incorporated herein by reference) discloses gastro-retentive dosage forms for prolonged delivery of levodopa and carbidopa / levodopa combinations. The dosage forms comprise a tablet containing the active ingredient and a gas-generating agent sealed within an expandable, hydrophilic, water-permeable and substantially gas-impermeable membrane. Upon contact with gastric fluid, the membrane expands as a result of the release of gas from the gas-generating agent in the tablet. The expanded membrane is retained in the stomach for a prolonged period of time up to 24 hours or more during which period the active ingredient is released from the tablet providing delivery of levodopa to the site of optimum absorption in the upper small intestine. For example, the application discloses a gastro-retentive dosage form of levodopa for oral administration to a patient in need thereof, the dosage form comprising (a) a tablet comprising a therapeutically effective amount of levodopa, a binder, and a pharmaceutically-acceptable gas-generating agent capable of releasing carbon dioxide upon contact with gastric juice, and (b) an expandable, hydrophilic, water-permeable and substantially gas-impermeable, membrane surrounding

the tablet, wherein the membrane expands as a result of the release of carbon dioxide from the gas-generating agent upon contact with the gastric juice, whereby the dosage form becomes too large to pass into the patient's pyloric sphincter. The dosage form may further comprise a covering (*e.g.,* a dry-fill capsule) for containing the dosage form, wherein the covering disintegrates upon contact with gastric fluid. The membrane may comprise polyvinyl alcohol. The gas-generating agent may be sodium bicarbonate, sodium carbonate, sodium glycine carbonate, potassium carbonate, calcium carbonate, magnesium carbonate or mixtures thereof. The binder may be a polyoxyethylene stearate, a poloxamer, a polyethylene glycol, a glycerol palmitostearate, a glyceryl monostearate, a methylcellulose or a polyvinyl pyrrolidone, such as Myrj 52, Lutrol F68, PEG 3350, a methylcellulose or a polyvinyl pyrrolidone.

Other exemplary dosage forms that may be adapted according to the teachings of the instant invention include US20030228360A1 and US20040052843.

VI. *Exemplary Delivery Devices*

Various amounts of the subject drugs or pharmaceutical compositions can be included in tablets and drug eluting devices of the invention. Such tablets and drug eluting devices typically contain at least 1 mg of a drug / pharmaceutical composition. These tablets and drug eluting devices can also contain at least 2 mg, at least 5 mg, at least 10 mg, at least 25 mg, at least 50 mg, at least 100 mg, at least 500 mg or at least 1000 mg of a drug / pharmaceutical composition.

Any of the devices discussed below can be used to administer carbidopa, levodopa, or combinations of these drugs as discussed above, or they can be used to deliver any other drug desired to be administered, *e.g.*, to treat any medical condition or disease state, or for any therapeutic or diagnostic purpose. In general, drugs / pharmaceutical compositions suitable for use herein can be small organic molecules (*e.g.*, non-polymeric molecules having a molecular weight of 2000 amu or less, such as 1000 amu or less), peptides or polypeptides and nucleic acids.

More than one type of drug can be present in a tablet or a drug eluting device of the invention. The drugs can be evenly distributed throughout a medicament or can be heterogeneously distributed in a medicament, such that one drug is fully or partially released before a second drug. See different embodiments of the drug devices and/or layering in other parts of this specification.

Dosage forms of the invention typically weigh at least 5 mg. Dosage forms (such as

the various shell designs of the invention) can also weigh at least 10 mg, at least 15 mg, at least 25 mg, at least 50 mg, at least 100 mg, at least 500 mg or at least 1000 mg.

Dosage forms of the invention typically measure at least 2 mm in one direction. For example, dosage forms can measure at least 5 mm, at least 10 mm, at least 15 mm or at least 20 mm in one direction. Typically, the diameter of the dosage forms is 2 to 40 mm, preferably 10 to 30 mm such as 20 to 26 mm. Mini-tablets have a diameter of 2 mm to about 5 mm. Such dosage forms can measure at least 2 mm, at least 5 mm, at least 10 mm, at least 15 mm or least 20 mm in a second direction and, optionally, a third direction. Preferably, the dosage form is of a size that facilitates swallowing by a subject.

The volume of a typical dosage form of the invention is at least 0.008 mL, at least 0.01 mL, at least 0.05 mL, at least 0.1 mL, at least 0.125 mL, at least 0.2 mL, at least 0.3 mL, at least 0.4 mL or at least 0.5 mL.

To produce a dosage form that can release at least two or three drugs at two or three different rates, and with preprogrammed delays, special dosage forms are used. For example, in the embodiments of the invention wherein levodopa, carbidopa, and the transport inhibitors are designed to be released concomitantly, the drugs may be formulated as bilayer (or other multilayer) tablets or shells (*e.g.*, stacked layer of cakes, each may represent an independent formulation). Alternatively, levodopa and carbidopa may be formulated as a tablet within a tablet or bead (not limited to two nested layers). The outer tablet may contain a levodopa / carbidopa combination designed to be released together either as immediate release delivery patterns or as a sustained release delivery. The inner tablet / bead may be formulated to release after the outer tablet / bead has released the formulations. Optionally, the inner tablet(s) / bead(s) may be formulated with a coating layer to help achieve the desired delay in time.

In certain embodiments, the drugs may be formulated into a core tablet held in a recessed fashion within an annular ring of drug material. Such a dosage form is described in U.S. patent application Ser. No. 10/419,536 entitled "Dosage Form with a Core Tablet of Active Ingredient Sheathed in a Compressed Angular Body of Powder or Granular Material, and Process and Tooling for Producing It," filed on Apr. 21, 2003 and Ser. No. 10/379,338 entitled "Controlled Release Dosage Forms," filed on Mar. 3, 2003 and are incorporated herein by reference. The outer annular ring is formulated with the levodopa and decarboxylase enzyme inhibitor and formulated for either immediate release or sustained release delivery for the desired time. The inner core(s) of the dosage form contain the

dopamine transport inhibitor to be released after a delay which may be formulated for the desired release profile.

Other embodiments of the invention use the dosage form described in U.S. patent application Ser. No. 10/191,298 entitled "Drug Delivery System for Zero-order, Zero-Order Biphasic, Ascending or Descending Drug Delivery," filed on Jul. 10, 2002, incorporated herein by reference. The dopamine transport inhibitor may be formulated in the tablet mantle and released at the desired rate after a delay. The levodopa and decarboxylase enzyme inhibitor may be formulated in the expanding plug and released at the desired rate upon entry into the stomach.

Another embodiment of this invention may be achieved by formulating each of the drugs as pellets / beads, each with its own release profile and delay where applicable, and delivering the mixture of the three pellets in a shell using methods commonly known in the art. Furthermore, the proportions of the different types of pellets / beads may be altered or customized by a skilled artisan (*e.g.*, qualified physician or pharmacologist), based on an individual patient's conditions, such as weight, age, gender, ethnicity, and/or specific genetic backgrounds. Such customization may be effected with the aid of, or automatically executed by a computer program based on relevant parameters such as those described above.

Embodiments of the invention wherein each drug may be released at a different rate can be formulated as tri-layer (or multilayer if necessary) tablets. Each layer of the tablet may have a distinct release profile. For example, a tablet within a tablet with an immediate release coating wherein the innermost tablet would be formulated with the dopamine transport inhibitor, the outer portion of the tablet formulated with levodopa, and the outer coating formulated with decarboxylase enzyme inhibitor, in an appropriate ratio according to the teachings of the instant invention. In another preferred embodiment, the drugs may be formulated into tablets held in a recessed fashion within an annular ring of drug material, as described above. The recessed core may be formulated as a delayed release of dopamine transport inhibitor at the desired release profile; the annular ring may be formulated to give the desired release profile of levodopa (immediate release and sustained release delivery); and an outermost coating layer may give an immediate release of decarboxylase enzyme inhibitor.

Another embodiment uses the delivery system as described in U.S. patent application Ser. No. 10/191,298, wherein the dopamine transport inhibitor is formulated in

the mantle and the expanding plug is a bilayer tablet. One layer of the bilayer tablet comprising levodopa formulated for sustained release delivery and the other layer comprising decarboxylase enzyme inhibitor formulated to release at the desired rate. Yet another embodiment of the invention could be achieved by formulating each of the drugs as pellets each with its own release profile and delay where applicable and delivering the mixture of the three pellets in a shell as commonly understood by one of ordinary skill in the art.

In yet another example, the tablet is a longitudinally compressed tablet containing a plurality of precompressed inserts of the various compositions of the invention, mixtures thereof, excipients, and optionally a permeation enhancer. The precompressed inserts may each have different compositions (*e.g.*, the top insert may constitute the first IR portion, the next one or more inserts may constitute the substantially zero-order release rate second portion, *etc.* Drug is only released at the edge or surface of this tablet, which can result in zero-order kinetics in, for example, the second portion. In certain embodiments, the tablet may be encased in a sheath or shell, which has an insoluble, impermeable plug at one end to seal off the end, and has an opening (*e.g.*, orifice) at the opposite end to allow drug release from successive layers of inserts (see **Figure 1**). The thickness of each insert may be adjusted to accommodate different dosages. The overall shape of the device is not necessarily cylindrical, cubic column, *etc.*, but can be any desired shape or size.

In certain embodiments, the tablet is a trilayer tablet having an inner core that includes one or more drugs in an appropriate matrix of excipients (*e.g.*, HPMC, MCC, lactose) and is surrounded on two sides by a bioadhesive polymeric coating. Preferred bioadhesive polymeric coatings are a DOPA-BMA polymer and a mixture of poly(fumaric-co-sebacic) anhydride and EUDRAGIT™ RS PO. Other bioadhesive polymers are described in the section below.

In another example, the tablet is comprised of a multiplicity of bioadhesive-coated microspheres or beads that have been compressed into a tablet core and subsequently coated with a bioadhesive coating and one or more additional coatings (*e.g.*, enteric coatings). For example, in an illustrative embodiment as shown in **Figure 2**, different types of beads, each type with separate types and/or thickness of coatings, may be mixed together in desired or customized proportions to deliver varying amounts of first IR, second portion of zero-order release, and optionally second portion of IR, *etc.* The coatings on different types of beads may control the release timing of each type of beads.

Various drug-eluting devices are described in U.S. Patent Nos. 4,290,426, 5,256,440, 5,378,475, 5,773,019 and 6,797,283, the contents of which are incorporated herein by reference.

In one example, the drug-eluting device includes an inner reservoir comprising the effective agent; a first coating layer, which is essentially impermeable to the passage of the effective agent; and a second coating layer, which is permeable to the passage of the effective agent. The first coating layer covers at least a portion of the inner reservoir; however, at least a small portion of the inner reservoir is not coated with the first coating layer (*e.g.*, there are one or more pores in the first coating layer). The second coating layer essentially completely covers the first coating layer and the uncoated portion of the inner reservoir. Typically, the first coating layer is a non-bioerodable or a slowly bioerodable polymer (*e.g.*, a polymer having a polymethylene backbone). For the present invention, one illustrative embodiment is shown in **Figure 3**, where the first coating is the bioadhesive coating, and the second coating is the first IR portion. The inner reservoir contains the second zero-order release portion, which may comprise one or a few layers to effect, for example, changing ratios of levodopa / carbidopa. One of these layers may also be the 3rd IR portion or the dopamine transporter inhibitor (see **Figure 4**).

In another example, the drug eluting device includes a multilayer core, often bilayer or more layers, formed of polymer matrices that swell upon contact with the fluids of the stomach or other GI fluids. At least one layer of the multilayer core includes a drug. A portion of the polymer matrices are surrounded by a band of insoluble material that prevents the covered portion of the polymer matrices from swelling and provides a segment of the dosage form that is of sufficient rigidity to withstand the contractions of the stomach. The core and the band of soluble material are coated with a bioadhesive polymeric coating. **Figure 5** provides an illustrative embodiment of this configuration. As shown, the three depicted layers represent the immediate-release composition layer (**IR**), and two substantially zero-order release rate composition layers (**CR1** and **CR2**). There may be more than two such substantially zero-order release rate composition layers, differing by their specific compositions (for example, the ratio of carbidopa / levodopa in the Parkinson disease therapeutic composition). A bioadhesive layer or patch (hatched lines) is shown to be on the outside wall of the shell encompassing the therapeutic compositions, which are successively released through an orifice close to the IR composition (proximal end).

In a further example, the drug eluting device is an osmotic delivery system.

Typically, the reservoir of such devices contains osmotic agents to draw water across a semi-permeable membrane and a swelling polymer to push drug out of the device at a controlled rate. For example, **Figure 5** shows that the distal end of the shell may comprise a plug that can push the therapeutic compositions towards the orifice at the proximal end. The push mechanism can be any suitable means, such as a water-absorbing gel that swells when in contact with aqueous solution, or a rigid plate / plunger that can be driven by a micromotor (optionally externally activated).

In yet another embodiment, there may be two or more reservoirs within a shell, each reservior coated by a bioadhesive layer as described above, and each reservior contains a different composition, such as different second doses designed to be released at successive times, or second zero-order release portion and the second IR portion (**Figure 6**).

In another embodiment (**Figure 7**), the composition may be formed as a cylinder or a column, or have a trapezoid profile (right panel). The compositions (*e.g.*, levodopa **72** and carbidopa **71**) are released starting from the top face and progressing in the order shown by the arrow. The top (beginning) of the dosage form has a different carbidopa / levodopa ratio from the bottom (end) of the dosage form.

In another embodiment (**Figure 8**), the first IR portion is formed as a layer, while one or more second portions (sustained zero-order release portion, *e.g.*, CR2) may be formulated as coated beads embedded in a layer of another sustained zero-order release sub-portion (*e.g.*, CR1). After the first IR portion is released, one sub-portion of the sustained zero-order release portion (*e.g.*, CR1) starts to release, while release of the other sub-portions (*e.g.*, CR2) is delayed due to the coating on the beads. There can be more than one layer and/or more than one types of beads according to this embodiment of the invention.

In another embodiment (**Figure 9**), the first IR portion **91** covers the bioadhesive layer **94**, which in turn covers the inner compositions, such as various sustained release (zero-order release) sub-portions (*e.g.*, **CR1 93**), and/or an optional ascending release portion (**92**), which may also be occupied by another sub-portion of sustained release (zero-order release). The first sub-portion of the zero-order release (**CR1 93**) may have a geometric shape (regular or irregular, symmetrical or asymmetrical) such that increasing or decreasing amounts of drugs may be released in unit time periods.

In another embodiment (**Figure 10**), drug release from the two sub-portions of zero-order release (**CR1 1002** and **CR2 1003**) is initiated from the inner core of a donut-shaped delivery device. After the outer IR layer **1001** is dissolved, holes on the bioadhesive layer

1004 encompassing the sub-portion(s) of zero-order release composition(s) may be release sequentially or simultaneously.

In another embodiment (**Figure 11**), the dosage form takes the shape of a rod, with the first IR portion **1101** situated at one or both ends (or on the surface (not shown)) of the rod. If there is one or more controlled release (zero-order release) sub-portion (such as **CR2 1103**), they are each sealed off by a substantially impermeable bioadhesive band **1104**, such that their release is delayed, until the other controlled release sub-portions (such as **CR1 1102**) are substantially completely released (see **Figure 11**).

Figure 12 shows yet another embodiment depicting a multilaminate bioadhesive buccal patch or tablet. The dosage form attaches to the mucosa surface (preferably through a bioadhesive layer attached to the **CR2** layer, optionally also the **CR1** layer, as described above), and sequentially releases the first IR **1202**, and one or more sub-portions (*e.g.*, **CR1 1203** and **CR2 1204**) of controlled release sub-portions of the zero-order release portion (second portion).

Figure 13 features a dose sipping system, where various types of beads corresponding to various sub-portions of controlled release (only two sub-portions, **CR1** and **CR2**, are shown as **1302**) are embedded in a matrix of the first IR portion **1301**, which in turn is deposited in a straw / tube. One end of the straw is sealed off by a porous plug **1303** to allow aqueous bodily fluid to seep in upon applying suction from the other end of the straw.

This embodiment also relates to a general concept for drug delivery, wherein a first portion of a multi-portion dosage form is formulated as a matrix for embedding one or more other portions of the same dosage form. In certain embodiments, the first portion is an immediate release (IR) formulation, and the other embedded portions are controlled release (CR) portions, each CR portion is optionally coated by a bioadhesive coat and/or a delayed release coat. Each CR portion may be formed as microparticles (*e.g.*, beads) suspended in the first portion (*e.g.*, IR portion) matrix. The disintegration of the matrix leads to the release of the embedded microparticles, which may re-adhere to the gut or other tissues (if coated by bioadhesive layer), and provided for sustained release.

This embodiment also relates to a general system for drug delivery, wherein therapeutic compositions are deposited at the end of a hollow tube sealed off by a porous plug. The plug holds the therapeutic compositions inside the tube, but is also porous enough to allow liquid to come into the tube through the plug if a vaccum is generated inside the

tube (such as by sipping or applying suction). The dissolved therapeutic compositions can then exit through the opposite end of the tube, *e.g.*, into the patient's mouth.

Figure 14 features a delivery device with a shell comprising a cap and a bioadhesive body. The cap is made of gelatin-type of material that is readily dissolved once the shell is internalized by a patient. The body of the shell comprises a bioadhesive material of the subject invention. Upon dissolution of the cap, the IR portion, and the substantially zero-order release portion (or sub-portions thereof) may be sequentially released as shown. Alternatively, the one or more CR sub-portions may be embedded within the IR matrix as described in other embodiments of the invention.

Figure 18 features yet another configuration of the delivery device, in which a **CR** portion **1801** is sandwiched between two adhesive layers **1802** (*e.g.*, a layered cross section) or inside one continuous adhesive layer **1802** (*e.g.*, configured as a filled tube). SPHEROMER™ I [p(FASA)] and SPHEROMER™ III are exemplary such bioadhesive layers (see, *e.g.*, Example 5). The portion / layer can (but need not) be substantially flat. In one embodiment, there are two substantially flat adhesive layers **1802** sandwiching one **CR** layer **1801**. Components of the **CR** can be either released from surfaces not in contact with the adhesive parts **1802**, and/or through the adhesive materials if such materials are at least partially permeable. An immediate release portion **IR 1803** is coated over all or a part of the adhesive layer **1802**. In one embodiment, the rapid dissolution of the **IR** portion exposes a **CR** surface not in contact with the adhesive material. In another embodiment, the dissolution of the **IR** portion does not substantially change the release rate of the **CR** portion. The tablet may be produced using methods such as those described in Examples 6-12.

Figure 19 features yet another configuration of the subject delivery device, which may be used in general to deliver any kind of drugs (or prodrugs, metablic precursors thereof, *etc.*). Although levodopa and/or carbidopa were used in the Examples to illustrate the delivery method, device and dosage form, it should be understood that the subject delivery devices (such as the one described in Figure 19), dosage form, and methods of making and using are not limited to these specific exemplary drug compositions described herein.

Thus according to this aspect of the invention, any drug to be delivered (*e.g.*, levodopa and/or carbidopa), optionally including a bioadhesive polymer composition, and/or pharmaceutically acceptable excipients, may be formulated using the subject

granulation-extrusion-spheronization process into multiparticulate pellets, which in turn may be dispersed in certain matrix materials, or simply encapsulated in capsules.

Specifically, appropriate amounts of the different ingredients are first weighed and mixed.

Suitable excipients for use in the subject granulation-extrusion-spheronization process include: Starcap-1500, starch-1500, and glycerine monostearate. In certain embodiments, the mixture is substantially free of microcrystalline cellulose.

In an exemplary embodiment, about 30-90%, about 40-85%, or about 50-80% (v/v) of the mixture (and the pellets formed therefrom) is effective ingredient (*e.g.*, drug composition), rather than excipients or polymers. Such loadings can be achieved using any drug or combination of drugs that are suitably cohesive, plastic, and engage in hydrogen bonding. Levodopa and carbidopa are examples of such drugs, though others will be known to or can be easily identified by those of skill in the art.

These different ingredients can then be blended together in any suitable device, such as a planetary type mixer (*e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for about 5-15 min.). Optionally, the blending process is done in small volume to reduce any possible loss of the ingredients due to their non-specific adherence to the blending device. The blending step is typically done to ensure the formation of a uniform dry mix of the ingredients, typically over a period of, *e.g.*, 5-15 min.

The dry mix is then granulated, *e.g.*, under low shear with a granulation fluid, so as to form a wet granulation. Granulation fluids may be purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone, *etc.*

In certain embodiments, the granulation process is conducted in a small volume, such as in a 500-mL cylindrical vessel.

In certain embodiments, the granulation process is conducted with manual mixing, or conducted mechanically, *e.g.*, in a planetary type mixer (such as a Hobart Mixer with a 5-qt mixing bowl). If the Hobart Mixer is used, it can be operated at its speed setting #1, depending on the batch size. Other types of mechanical mixers may also be used, with their respective appropriate settings, to achieve substantially the same result.

Once the wet granulation is formed, it may be extruded through the screen of a

screen-type extruder. In certain embodiments, a Caleva Model 20 (or Model 25) Extruder may be used, operating at 10-20 rpm, and forming breakable wet strands ("the extrudate"). The screen aperture may be set at 0.8, 1, or 1.5 mm. Other types of extruders may be used to achieve substantially the same result.

The extrudate may then be spheronized in a spheronizer. For example, a Caleva Model 250 spheronizer equipped with a 2.5-mm spheronization plate may be used, which may be operated at a speed of about 1000-2000 rpm, typically for 5-10 min., in order to form spheronized pellets. Other types of spheronizer may be used to achieve substantially the same result.

For certain effective ingredients, such as carbidopa, the extruding step and the spheronization step may be omitted.

The spheronized pellets may then be dried. The drying may be conducted in a fluidized bed drier, such as a Vector MFL.01 Micro Batch Fluid Bed System. If the Vector drier is used, it may be operated at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of about 50 °C. Alternatively, the pellets may be dried in an ACT (Applied Chemical Technology) fluidized bed drier, operating at an inlet air flow rate of 140-150 fpm (foot per minute) and an inlet air temperature of 104 °F. Other types of driers may also be used to achieve substantially the same result. Depending on the specific type of drugs / compositions, the drying temperature for a drier similar to the Vector drier may be between 35-70 °C, or 40-65 °C, or 45-60°C, or 45-55 °C, *etc.* The drying temperature for a drier similar to the ACT drier may be between 70-140 °F, or 80-130 °F, or 90-120°F, or 100-110 °F, *etc.*

In yet another embodiment, the spheronized pellets may be dried in an oven, such as a Precision gravity oven, operating at about 50 °C, for 4-48 hrs, or 8-24 hrs. Depending on the specific type of drugs / compositions, the oven drying temperature for a drier similar to the Precision gravity oven may be between 35-70 °C, or 40-65 °C, or 45-60°C, or 45-55 °C, *etc.*

The dried pellets may then be screened and/or classified. This can be done by using a stack of sieves, such as stainless steel sieves U.S. standard mesh sizes 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, or 60, *etc.*, and using a mechanical sieve shaker (*e.g.*, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min.). Particle size and distribution of pellet formulations can then be analyzed, and the classified pellets ranging from 0.25 mm (mesh # 60) to 2 mm (mesh # 10) may be selected for use or future formulation, such as additional

film coating or other experimentation.

In certain embodiments, the formed pellets may be film-coated, *e.g.*, with a delayed-release coating (such as an entaric coating), a controlled-release (CR) coating, a bioadhesive polymeric composition, and/or a dispersion-promoting coating, *etc.*

For example, the pellet core may be optionally surrounded by a CR coating, such as polymeric substance based on acrylates and/or methacrylates, *e.g.*, a EUDRAGIT™ polymer (sold by Rohm America, Inc.). Specific EUDRAGIT™ polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGIT™ RL, EUDRAGIT™ NE, and EUDRAGIT™ RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT™ RL is freely permeable and EUDRAGIT™ RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGIT™ L is pH dependent. EUDRAGIT™ L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable. If desired, two or more types of polymeric substances may be mixed for use as the CR coating. Other polymers suitable for CR coatings, such as ethyl cellulose and cellulose acetate, can also be used in the CR coating. In certain embodiments, the CR coating may comprise one or more suitable polymers, such as a combination of two or more of the polymers discussed above.

Optionally, the pellets may also be coated by a bioadhesive polymeric composition. The adhesive material may facilitate the adhesion of the pellets to a desired surface, such as a preferred GI tract surface. For example, the pellets / beads may be coated by a top-layer of a bioadhesive polymer such as SPHEROMER™ I [p(FASA)], SPHEROMER™ II, SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof (see, *e.g.*, Example 14).

In certain embodiments, the functions of a CR coating and bioadhesive coating can be combined in a single layer by using a mixture of polymers including a bioadhesive polymeric material and a polymer suitable for controlled release, *i.e.*, a single layer may be both the CR layer and the bioadhesive layer of a particle.

Optionally, the pellets can also be film-coated with an additional layer of a so-called "non-functional polymer," such as OPADRY™ II, EUDRAGIT™ E, ACRYL-EZE™, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol,

polyvinylacetate, polyanhydride, *etc.* (see, *e.g.*, Example 14). This layer may serve as a dispersion-promoting coating that inhibits clumping and aggregation of the particles during dispersion. In embodiments wherein the pellets are further compressed with excipients to form tablets, this layer is preferably sufficiently strong or resilient to remain substantially intact during the compression process. This layer may also be protected by including a cushioning material among the excipients of the tablet matrix such as spray dried lactose, various grades of microcrystalline cellulose, glyceryl monostearate, pregelatinized starch, compressible sugar, PEG 8000, dicalcium phosphate (Di-Tab), calciumhydrogenphosphate (Bekapress D2) and cellactose.

The coating material (such as bioadhesive polymeric materials and/or functional / nonfunctonal polymers) may be dissolved in an appropriate solvent, such as methylene chloride (*e.g.*, for SPHEROMER™ I), methanol (*e.g.*, for SPHEROMER™ III), a binary mixture of methanol and methylene chloride (*e.g.*, for SPHEROMER™ I and SPHEROMER™ III), methanol or a binary mixture of ethanol and water (3:1 v/v) (*e.g.*, for SPHEROMER™ IV), or methanol, ethanol, or isopropanol, or their binary mixture with acetone (*e.g.*, functional or non-functional polymer).

The film coating may be performed in a fluidized bed coater, such as a Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liters per minute), and an inlet air temperature of about 25-45 °C, or about 30-40 °C, depending on the specific drugs and coatings (*e.g.*, 25-30 °C for SPHEROMER™ I-coated levodopa-carbidopa; about 35 °C for SPHEROMER™ III-coated levodopa-carbidopa, *etc.*). If the Vector System is used, the pellets may be pre-warmed at 35 °C for 2-5 min., and after film-coating, post-dried at about 30 °C for about 15-30 min.

Alternatively, pellets may be coated in a fluid bed processor, such as a Fluid Air Model 5 fluid bed processor equipped with a Wurster insert, operating at an inlet air flow rate of about 70 cfm (cubic foot per minute) and an inlet air temperature of about 35 °C. For this type of fluid bed processor, the pellets may be pre-warmed at 40 °C for 5-7 min., and after film-coating, post-dried at about 35 °C for about 30 min.

Other types of coaters may also be used to achieve substantially the same result.

Different lots or even different types of the same pellets produced using the subject method may optionally be mixed, *e.g.*, by using a blender (such as a GlobePharma Maxiblend Blender equipped with an 8-qt stainless steel V-shell).

In certain embodiments, different types of pellets may be mixed. For example, some pellets may have no coating and are simply a core comprising the effective ingredients. Other pellets, even if identically in core structure, may further be coated by one or more types of coatings, *e.g.*, bioadhesive coating, delayed-release coating, controlled-release coating, and/or dispersion-promoting coating, *etc.*

In certain embodiments, pellets produced using the methods of the invention may be encapsulated in capsules, such as hard gelatin capsules or pullulan capsules (NPcaps™), each with a predetermined amount of effective ingredients. For example, if the effective ingredients are carbidopa and levodopa, 50 mg carbidopa and 200 mg of the levodopa may be encapsulated.

In certain embodiments, pellets produced using the methods of the invention may be dispersed in a matrix material to assist the delivery of the effective ingredients of the pellets. There are at least two preferred configurations according to this embodiment of the invention.

Figure 19 shows a schematic drawing (not to scale) of one such configuration. In Figure 19, the active components **1901** (such as the pellets produced using the subject method, which are not necessarily round in shape) are embedded / dispersed within an inactive material or carrier matrix **1902**. The carrier matrix **1902** can rapidly disintegrate, *e.g.*, dissolve substantially completely (superdisintegrant) within about 15 minutes, 10 minutes, 8 minutes, 7 minutes, 6 minutes, 5 minutes, 3 minutes, 2 minutes, or about 1 minute or less. See, *e.g.*, Example 15.

The inactive material **1902** may additionally comprise one or more cushioning materials dispersed throughout, *e.g.*, sufficient to protect the active components **1901** when preparing the delivery device, by substantially absorbing the impact of compacting, and/or reducing friction on the surface of the particles **1901** (to prevent damaging the substructure of the particles, see below).

In certain embodiments, in order to incorporate these particles into a tablet matrix, a filler/binder must be used in the tableting process that will not allow the destruction of the pellets during the tableting process. Materials that are suitable for this purpose include, but are not limited to, microcrystalline cellulose (AVICEL®), soy polysaccharide (EMCOSOY®), pre-gelatinized starches (STARCH® 1500, NATIONAL® 1551), and polyethylene glycols (CARBOWAX®). These materials may be present in the range of about 5%-75% (w/w), and preferably between about 25%-50% (w/w).

In addition, disintegrants are added to the tablets in order to disperse the beads once the tablet is ingested. Suitable disintegrants include, but are not limited to: crosslinked sodium carboxymethyl cellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®, PRIMOJEL®), and crosslinked polyvinylpolypyrrolidone (Plasone-XL). These materials may be present in the range of about 3%-15% (w/w), with a preferred range of about 5%-10% (w/w).

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, and hydrogenated vegetable oil. These lubricants should be present in amounts from about 0.1%-10% (w/w), with a preferred range of about 0.3%-3.0% (w/w).

The particles **1901** may be in any suitable size and shape (rods, beads, or other regular or irregular shapes). In one embodiment, the particles are beads with a diameter of less than about 2 mm, about 1.5 mm, about 1 mm, about 0.8 mm, about 0.7 mm, about 0.5 mm, about 0.3 mm, or about 0.1 mm. In certain embodiments, the pellets are substantially homogeneous in size and/or shape. In certain embodiments, for pellets with levodopa and/or carbidopa as effective ingredient, the pellet size is about 0.8 – 1 mm. Particles are formulated to these sizes in order to enable high drug loading when needed.

As described above, particles **1901** may have substructures, such as various coating layers surrounding a drug / prodrug core. Although the following describes the substructures using a bead with levodopa and/or carbidopa as effective ingredient, it is an illustrative example only, and the description also applies to other shapes of particles with other effective ingredients.

The core by itself may be an immediate release portion, or may have release-controlling components (*e.g.*, CR portion), and preferably, the core is made by extrusion, such as the granulation-extrusion-spheronization process described in, *e.g.*, Example 13. The core is optionally surrounded by a CR coating, such as polymeric substance based on acrylates and/or methacrylates, *e.g.*, a EUDRAGIT™ polymer (sold by Rohm America, Inc.). Specific EUDRAGIT™ polymers can be selected having various permeability and water solubility, which properties can be pH dependent or pH independent. For example, EUDRAGIT™ RL, EUDRAGIT™ NE, and EUDRAGIT™ RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, which are present as salts and give rise to the permeability of

the lacquer films. EUDRAGIT™ RL is freely permeable and EUDRAGIT™ RS is slightly permeable, independent of pH. In contrast, the permeability of EUDRAGIT™ L is pH dependent. EUDRAGIT™ L is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water, but becomes increasingly soluble in a neutral to weakly alkaline solution by forming salts with alkalis. Above pH 5.0, the polymer becomes increasingly permeable. If desired, two or more types of polymeric substances may be mixed for use as the CR coating. Other polymers suitable for CR coatings, such as ethyl cellulose and cellulose acetate, can be used in the CR coating. The CR coating may comprise one or more suitable polymers, such as a combination of two or more of the polymers discussed above.

Optionally, the CR coating is itself coated by a layer of adhesive material that facilitates the adhesion of the particles / beads to a desired surface, such as a preferred GI tract surface. Various suitable adhesive materials are described herein above. For example, the pellets / beads may be coated by a top-layer of a bioadhesive polymer such as SPHEROMER™ I [p(FASA)], SPHEROMER™ III, SPHEROMER™ IV, or mixtures thereof (see, *e.g.*, Example 14). In certain embodiments, the functions of a CR coating and bioadhesive coating can be combined in a single layer by using a mixture of polymers including a bioadhesive polymeric material and a polymer suitable for controlled release, *i.e.*, a single layer may be both the CR layer and the bioadhesive layer of a particle.

Optionally, pellets can be further film-coated with an additional layer of a so-called "non-functional polymer" such as OPADRY™ II, EUDRAGIT™ E, ACRYL-EZE™, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinylacetate, polyanhydride, *etc.* (see, *e.g.*, Example 14). This layer may serve as a dispersion-promoting coating that inhibits clumping and aggregation of the particles during dispersion. In embodiments wherein the pellets are further compressed with excipients to form tablets, this layer is preferably sufficiently strong or resilient to remain substantially intact during the compression process. This layer may also be protected by including a cushioning material among the excipients of the tablet matrix such as spray dried lactose, various grades of microcrystalline cellulose, glyceryl monostearate, pregelatinized starch, compressible sugar, PEG 8000, dicalcium phosphate (Di-Tab), calciumhydrogenphosphate (Bekapress D2) and cellactose, *e.g.*, so that the the outer layer is not significantly scratched or gouged during the compression process, and/or retains its dispersion-promoting properties.

Optionally, an **IR** portion is included in the particle, such as over the dispersion-promoting coating, or between the dispersion-promoting coating and the adhesive layer, *etc.*

In an alternative embodiment, particles **1901** are not embedded within the inactive material **1902**, but are instead disposed loose in a capsule that dissolves and releases the particles in the GI tract.

It should be understood that any other embodiments of the invention, such as those utilizing beads / pellets (see *e.g.*, Figures 2, 8, 13, *etc.*), may additionally or alternatively use the coated pellets shown in Figure 19.

Figure 20 features yet another embodiment of the delivery device, in which particles described herein above (*e.g.*, with respect to Figure 19) are embedded within a slow eroding material **2001** (*e.g.*, that gradually erodes over 30 minutes, 45 minutes, 1 hr, 2 hrs, 4 hrs, 6 hrs, or longer). At least a portion of the eroding material **2001** is covered by an **IR** portion **2002**, which disintegrates relatively rapidly to expose a surface of eroding material **2001**. A portion of the slow eroding material **2001** is also optionally covered by a passive polymer support layer and/or an adhesive material **2003** as described herein above. In certain embodiments, the IR portion **2002** may be disposed on the adhesive layer **2003** instead of the eroding material 2001 as depicted. See, *e.g.*, Example 16.

According to a related aspect of the invention, any drug to be delivered (*e.g.*, levodopa and/or carbidopa), optionally including a bioadhesive polymer composition, and/or pharmaceutically acceptable excipients, may also be formulated as a multilayer tablet.

Specifically, different ingredients (such as those described above) are weighed and mixed. These ingredients, possibly with the exception of any lubricants, can then be blended together in any suitable device, such as an end-over-end ATR rotator (*e.g.*, model RKVS), or a planetary type mixer (*e.g.*, Hobart Mixer). Optionally, the blending process is done in small volume to reduce any possible loss of the ingredients due to their non-specific adherence to the blending device. The blending step is typically done to ensure the formation of a uniform dry mix of the ingredients, typically over a period of, *e.g.*, 5-15 min.

The dry mix is then granulated, *e.g.*, under low shear with a granulation fluid, so as to form a wet granulation. Granulation fluids may be purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of

a polymeric composition in a chlorinated solvent or in a ketone, *etc.*

In certain embodiments, the granulation process is conducted in a small volume, such as in a 500-mL cylindrical vessel.

In certain embodiments, the granulation process is conducted with manual mixing, or conducted mechanically, *e.g.*, in a planetary type mixer (such as a Hobart Mixer with a 5-qt mixing bowl). If the Hobart Mixer is used, it can be operated at its speed setting #1, depending on the batch size. Other types of mechanical mixers may also be used, with their respective appropriate settings, to achieve substantially the same result.

Once the wet granulation is formed, it is dried. In certain embodiments, the wet granulation is dried in an oven (*e.g.*, a Precision gravity oven, operating at about 50 °C, for 8-24 hrs; or similar appropriate conditions for other types of ovens). Alternatively, the granulation may be dried in a fluidized bed drier, such as a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of about 50 °C. The drying temperature is generally around 50 °C. However, depending on different types of drugs / compositions, the temperature may be 35-70 °C, or 40-65 °C, or 45-60°C, or 45-55 °C, *etc.*

The dried granulation is then ground, *e.g.*, by using a pestle in a mortar, optionally followed by sieving the ground material, *e.g.*, through an approrpiate-sized screen (such as a U.S. Std. mesh # 60 screen), depending on the desired size of the granules.

At this point, the sieved granulation may be blended with a lubricant. In certain embodiments, the blending is conducted using an end-over-end ATR rotator (*e.g.*, model RKVS). In certain embodiments, the blending is conducted using a planetary type mixer (*e.g.*, Hobart Mixer, operating at the speed setting #1, for 5-15 min.). As a result, a uniformly lubricated dry mix is formed, which is then ready for compression.

Optionally, before compression, the lubricated dry mix may be passed through a sieve or screen, *e.g.*, a U.S. Std. mesh # 60 screen.

Different components of the pharmaceutical composition (*e.g.*, the effective ingredients, any bioadhesive polymeric materials, or other coatings, *etc.*) may be prepared as a mixture or separately using the subject methods. Once the dry mixes are formed, they can be compressed into single layer or multilayer tablets. For example, the lubricated dry mix may be pressed into tablets, such as by using a single-station manual tablet press (*e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set). If the GlobePharma machine is used, tablets may be prepared, *e.g.*, at a

pressure ranging from 250 to 4000 pounds per square inch (psi), and a compression time of, *e.g.*, 1 to 4 seconds. Other machines may also be used to achieve substantially the same result.

Alternatively, in certain embodiments, tablets may be produced with wet granulation of active ingredients followed by direct compression (see, *e.g.*, Example 6).

In certain embodiments, multilayer tablets may be produced, with each layer comprising a different ingredient. In these embodiments, a single-station manual tablet press (*e.g.*, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with adequate die and punch set) may be used in several steps to produce the multilayer tablets. For example, for a bilayer tablet, the compression process may include:

(1) adding the first layer blend into the die cavity, optionally followed by manually tapping it, *e.g.*, using a stainless steel spatula;

(2) adding the second layer blend into the die cavity;

(3) pre-compressing the two layers together, *e.g.*, at a pressure ranging from 250 to 500 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 5 seconds.

(4) compressing the pre-compacted layers together, *e.g.*, at a pressure ranging from 1000 to 4000 pounds per square inch (psi) and a compression time of, *e.g.*, 1 to 4 seconds.

The process can be repeated or modified if more than two layers of ingredients are to be used.

In certain embodiments, the tablet can be made with a pre-compressed insert with effective ingredients. Such pre-compressed inserts may be produced with direct compression (see, *e.g.*, Example 10). The same press machine may be used for this process. For example, if using the GlobePharma Manual Tablet Compaction Machine MTCM-I machine, tablet inserts may be prepared, *e.g.*, at a pressure ranging from 500 to 1000 pounds per square inch (psi), and a compression time of, *e.g.*, 1 to 2 seconds. Other machines may also be used to achieve substantially the same result. The pre-compressed insert may be used as one of the layers (*e.g.*, the second layer) in the tablet, or embedded in the middle of another layer (*e.g.*, the second layer). See, for example, Example 10.

Optionally, the tablets may be coated with one or more coating compositions, such as in the form of successive layers. The coating compositions may include bioadhesive layers, delayed release layers, controlled-release layers, and/or other functional / non-functional polymers *etc.* (*supra*). For example, tablets may be film-coated for this purpose,

using a pan coater (*e.g.*, O'Hara Labcoat, operating at an inlet air flow rate of about 60 cfm (cubic foot per minute) and an inlet air temperature of about 35 °C). The tablets may be pre-warmed at 35 °C for 5-10 min., and after film coating, may be post-dried at about 30 °C for about 15-30 min. Other coaters may also be used to achieve substantially the same result.

Figure 21 features yet another embodiment of the delivery device, in which particles **2100** described herein above (*e.g.*, with respect to Figure 19) are dispersed on the surface of a bioadhesive film **2101**. The film may optionally be dried or cured, *e.g.*, without disrupting the particle adhesion. The film may then be placed in a capsule **2102** for administration to a patient. If needed, the film may first be folded or cut to a suitable shape or size. Once administered to a patient, the capsule releases the film, which then rehydrates (if necessary) and adheres to a mucosal surface, allowing the particles spreaded and adhered thereto to release the active components.

In certain embodiments, the subject composition is formulated for variable dosing, such as customized dosing for individual patients.

In addition, more than one type of drugs can be present in a tablet or a drug eluting device of the invention, *e.g.*, for combination therapy with other pharmaceutical compositions effective for treating PD or other movement disorders (see below). The drugs can be evenly distributed throughout a medicament or can be heterogeneously distributed in a medicament, such that one drug is fully or partially released before a second drug. See different embodiments of the drug devices and/or layering in other parts of this specification.

Dosage forms of the invention typically weigh at least about 50 mg. Dosage forms (such as the various shell designs of the invention) can also weigh at least 100 mg, at least 150 mg, at least 250 mg, at least 500 mg, or at least 1000 mg, *etc.*

Dosage forms (*e.g*, capsule or tablet) of the invention typically measure at least 2 mm in one direction. For example, dosage forms can measure at least 5 mm, at least 10 mm, at least 15 mm or at least 20 mm in one direction. Typically, the diameter of the dosage forms is 2 to 40 mm, preferably 10 to 30 mm such as 20 to 26 mm. Mini-tablets have a diameter of 2 mm to about 5 mm. Such dosage forms can measure at least 2 mm, at least 5 mm, at least 10 mm, at least 15 mm or least 20 mm in a second direction and, optionally, a third direction. Preferably, the dosage form is of a size that facilitates swallowing by a subject.

The volume of a typical dosage form of the invention is at least 0.008 mL, at least

0.01 mL, at least 0.05 mL, at least 0.1 mL, at least 0.125 mL, at least 0.2 mL, at least 0.3 mL, at least 0.4 mL or at least 0.5 mL.

Dosage forms of the invention may be a tablet that can be of any suitable size and shape, for example, round, oval polygonal or pillow-shaped, and optionally bears nonfunctional surface markings. Especially in the case of coated tablets, they are preferably designed to be swallowed whole and are therefore typically not provided with a breaking score. Tablets of the invention can be packaged in a container, *e.g.*, accompanied by a package insert providing pertinent information such as, for example, dosage and administration information, contraindications, precautions, drug interactions and adverse reactions.

To produce a dosage form that can release at least two or three drugs at two or three different rates, and with preprogrammed delays, special dosage forms are used. For example, in the embodiments of the invention wherein different dosage forms of levodopa / carbidopa are designed to be released concomitantly, the drugs may be formulated as bilayer (or other multilayer) tablets or shells (*e.g.*, stacked layer of cakes, each may represent an independent formulation). Alternatively, the drugs may be formulated as a tablet within a tablet or bead (not limited to two nested layers). Optionally, a bioadhesive layer may be coated over part or all of a gel capsule (or other forms of delivery device) to enhance the stay of the device within a certain area of the GI tract, such as the intestine.

The various embodiments described herein are only a sample of numerous possible configurations to deliver the subject dosage forms. Other variations may be readily envisioned based on the principals and teachings of the instant specification. For example, various other drug-eluting devices are described in U.S. Patent Nos. 4,290,426, 5,256,440, 5,378,475, 5,773,019 and 6,797,283, the contents of which are incorporated herein by reference.

In these and other embodiments of the invention, the various bioadhesive coatings that can be used are described in detail in the section below.

Many of the different embodiments described above may be implemented by using rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a subject pharmaceutical composition at a particular target site. The biodegradable polymers undergo

chemical decomposition to form soluble monomers or soluble polymer units. The biodegradation of polymers usually involves chemically or enzymatically catalyzed hydrolysis. Representative biodegradable polymers comprise a member selected from biodegradable poly(amides), poly(amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(orthoesters), poly(anhydrides), biodegradable poly(dehydropyrans), and poly(dioxinones). The polymers are known to the art in Controlled Release of Drugs, by Rosoff, Ch. 2, pp. 53-95 (1989); and in U.S. Pat. Nos. 3,811,444; 3,962,414; 4,066,747; 4,070,347; 4,079,038; and 4,093,709.

In certain embodiments, representative dosage forms include hydrogel matrix containing a plurality of tiny pills or other particles. The hydrogel matrix comprises a hydrophilic polymer, such as selected from a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectin, amylopectin, gelatin and a hydrophilic colloid. The hydrogel matrix comprises a plurality of tiny pills or particles (such as 4 to 50), each tiny pill or particle may comprise a different portion of the subject compositions (*e.g.*, IR, *etc.*). Representative of wall-forming materials include a triglyceryl ester selected from glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl laureate, glyceryl didecenoate and glyceryl tridecenoate. Other wall forming materials comprise polyvinyl acetate phthalate, methylcellulose phthalate, and microporous vinyl olefins. Procedures for manufacturing tiny pills are disclosed in U.S. Pat. Nos. 4,434,153; 4,721,613; 4,853,229; 2,996,431; 3,139,383 and 4,752,470, which are incorporated by reference herein.

In still other embodiments, the invention employs a dosage form comprising a polymer that releases a drug by diffusion, flux through pores, or by rupture of a polymer matrix. The dosage form matrix can be made by procedures known to the polymer art. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier, like polyethylene glycol, with a known dose of the subject pharmaceutical composition, and adding it to a silastic medical grade elastomer with a cross-linking agent, like stannous octanoate, followed by casting in a mold. The step is repeated for each successive layer. The system is allowed to set, *e.g.*, for 1 hour, to provide the dosage form. Representative polymers suitable for manufacturing the dosage form include olefin and vinyl polymers, condensation polymers, carbohydrate polymers, and silicon polymers as represented by poly(ethylene), poly(propylene), poly(vinyl acetate), poly(methyl acrylate),